

Studies of a New Synthetic Route to
3H-Indol-3-one 1-N-oxides (Isatogens)

by

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Dedication

To my Parents for their patience and
understanding over many years.

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I would like to thank Dr. G. Tennant for supervision and his encouragement during the course of my research work.

I would also like to thank the University of Edinburgh for the provision of laboratory and library facilities. I am also grateful to the University of Edinburgh and the Department of Chemistry therein for their permission to engage in my research work on a part-time basis whilst employed by the University.

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Abstract

This thesis is concerned with the investigation of the novel acetic acid-catalysed cyclisation of 1-substituted 2-halogeno-2-(2-nitroaryl)ethanones as a general route to 2-substituted 3H-indol-3-one 1-N-oxides (isatogens), a relatively inaccessible class of indole derivatives. The discussion of the results obtained in this investigation is preceded by a survey of the relatively few literature methods for the synthesis of isatogens and also of their chemical reactivity and their biological activity.

As a preliminary to the investigation^{of} the scope of the acid-catalysed cyclisation of 1-aryl-2-halogeno-2-(2-nitroaryl)ethanones to 2-arylisatogens, methods for the synthesis of the key 1-aryl-2-(2-nitroaryl)ethanone starting-materials were evaluated. Successful methods employed included, Friedel-Crafts reactions of arenes with 2-nitroarylacetyl chlorides and the triethylamine-catalysed aroylation of 1-(N,N-dimethylamino)-2-(2-nitroaryl)ethenes. The former method was found to be more limited than the latter for the synthesis of 1-aryl-2-(2-nitroaryl)ethanones. Bromination of the latter compounds with bromine in 1,2-dimethoxyethane at room temperature provides a general method for the synthesis of 1-aryl-2-bromo-2-(2-nitroaryl)-ethanones. Heating these compounds in glacial acetic acid affords high yields of readily separated mixtures of the corresponding 2-arylisatogens and their 5-bromo derivatives. Formation of the latter compounds is largely suppressed

when cyclisation is carried out in the presence of hydroquinone.

The attempted acid-catalysed cyclisation of ethyl 3-bromo-3-(2-nitrophenyl)-2-oxopropanoate to 2-ethoxy-carbonyl isatogen was prevented by difficulties encountered in the synthesis of the bromo-ketoester starting-material.

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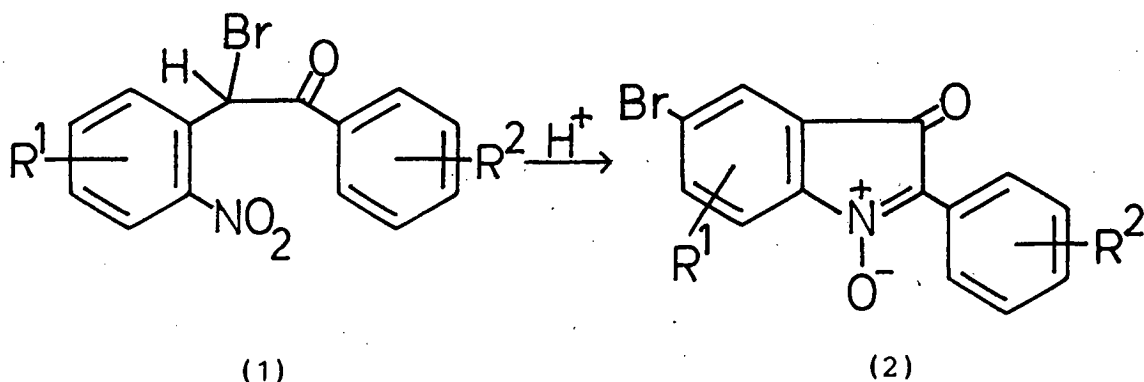
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BIBLIOGRAPHY

Preface

The following thesis is concerned with the investigation of a new general synthetic route to 3H-indol-3-one 1-N-oxide (isatogen) derivatives. These studies were prompted by previous work carried out in the Department of Chemistry, University of Edinburgh, which demonstrated (Scheme) that heating 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (1; $R^1=R^2=H$) in glacial acetic



Scheme

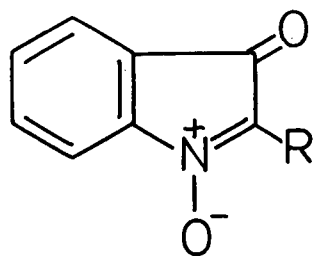
acid resulted in its cyclisation in high yield to 5-bromo-2-phenylisatogen (2; $R^1=R^2=H$). The objectives of the present studies were to evaluate the potential of this novel type of cyclisation for the general synthesis of 2-aryl-isatogens and to extend such reactions to the synthesis of other 2-substituted isatogen derivatives.

The results obtained in the present studies are discussed in chapter 2, and by way of introduction, this is preceded in chapter 1 by a survey of the relatively few literature methods available for the synthesis of ^3H -indol-3-one 1-N-oxides (isatogens) and also of their chemical reactivity and little known biological activity.

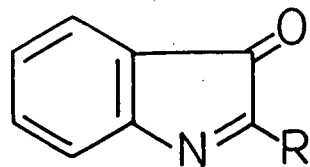
The nomenclature and numbering of the ring-systems involved in these studies strictly follow the format adopted by Chemical Abstracts.

CHAPTER 1

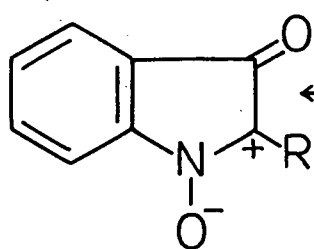
A Survey of the Synthesis, Chemical
Reactivity and Biological Properties
of 3H-Indol-3-one 1-N-Oxides (Isatogens)



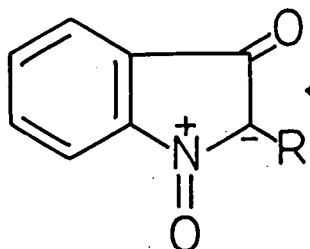
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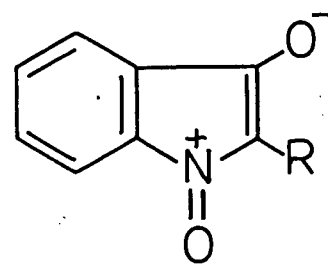
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(3)

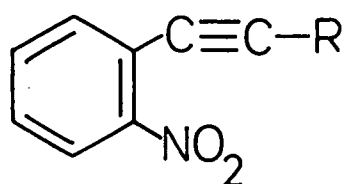


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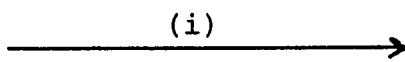


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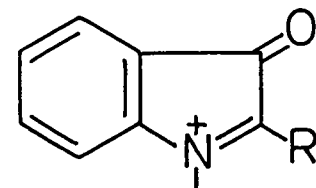
Scheme 1



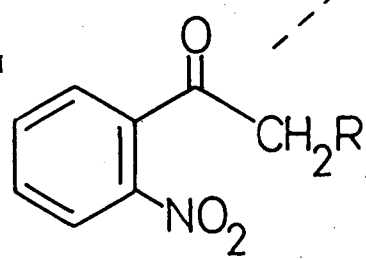
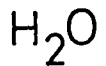
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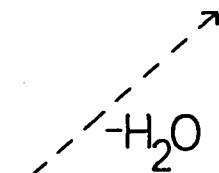
(i)



(7)



(8)



(i) conc. H_2SO_4 , room temp.

a; CO_2Et

b; $2\text{-NO}_2\text{C}_6\text{H}_4\text{C}\equiv\text{C}$

Scheme 2

A Survey of the Synthesis, Chemical Reactivity and
Biological Properties of 3H-Indol-3-one 1-N-oxides (
Isatogens)

3H-Indol-3-one 1-N-oxides or isatogens (Scheme 1; (1)) were first reported by Baeyer^{1,2} in 1881 during the course of his researches on indigo. They are typically brightly coloured red or orange crystalline solids that are not found naturally. The isatogens are very closely related structurally to 3H-indol-3-ones (2) which were first reported in 1912.³

The chemistry of the isatogens has been reviewed twice, firstly by Sumpter and Miller in 1954⁴ and then again by Hiremath and Hooper in 1978.⁵ The parent isatogen (1; R=H) is unknown and most of the isatogen derivatives known to date are 2-aryl compounds (1; R = aryl). 2-Alkyl-isatogens (1; R = alkyl) have been known only since 1974 and are obtained by a completely different synthetic route to that leading to their 2-arylisatogen counterparts.

Isatogens being indolone N-oxide derivatives (1) exhibit reactivity consistent with their formulation as resonance hybrids [(3)] \leftrightarrow [(4)] \leftrightarrow [(5)]. The contribution of the canonical form (3) to the mesomeric structure of the isatogens accounts for their tendency to undergo 1,3-dipolar cycloaddition reactions as discussed later.

Conversely, the back-polarisation represented by the canonical forms (4) and (5) accounts for the nitron/N-oxide⁶ like reactivity of isatogens.

The relatively few isatogen derivatives reported to date reflects the very limited number of methods available for their synthesis. Moreover, most of the available isatogen syntheses involve the intramolecular cyclisation of relatively inaccessible starting materials such as 2-nitrophenylacetylenes or halogenated 2-nitro-stilbene derivatives.

In the following survey the discussion of the principal synthetic methods for isatogens is followed by an outline of their typical chemical reactions and finally an indication of their known biological properties.

The Synthesis of Isatogens

Synthetic routes to isatogen derivatives fall into two broad categories depending on whether they involve intramolecular cyclisation reactions or are based on oxidative transformations of indole derivatives.

(a) Isatogen Syntheses Based on Intramolecular Cyclisation Reactions

Intramolecular cyclisation reactions of 2-substituted nitrobenzene derivatives constitute the largest group of transformations leading to isatogen derivatives. Such

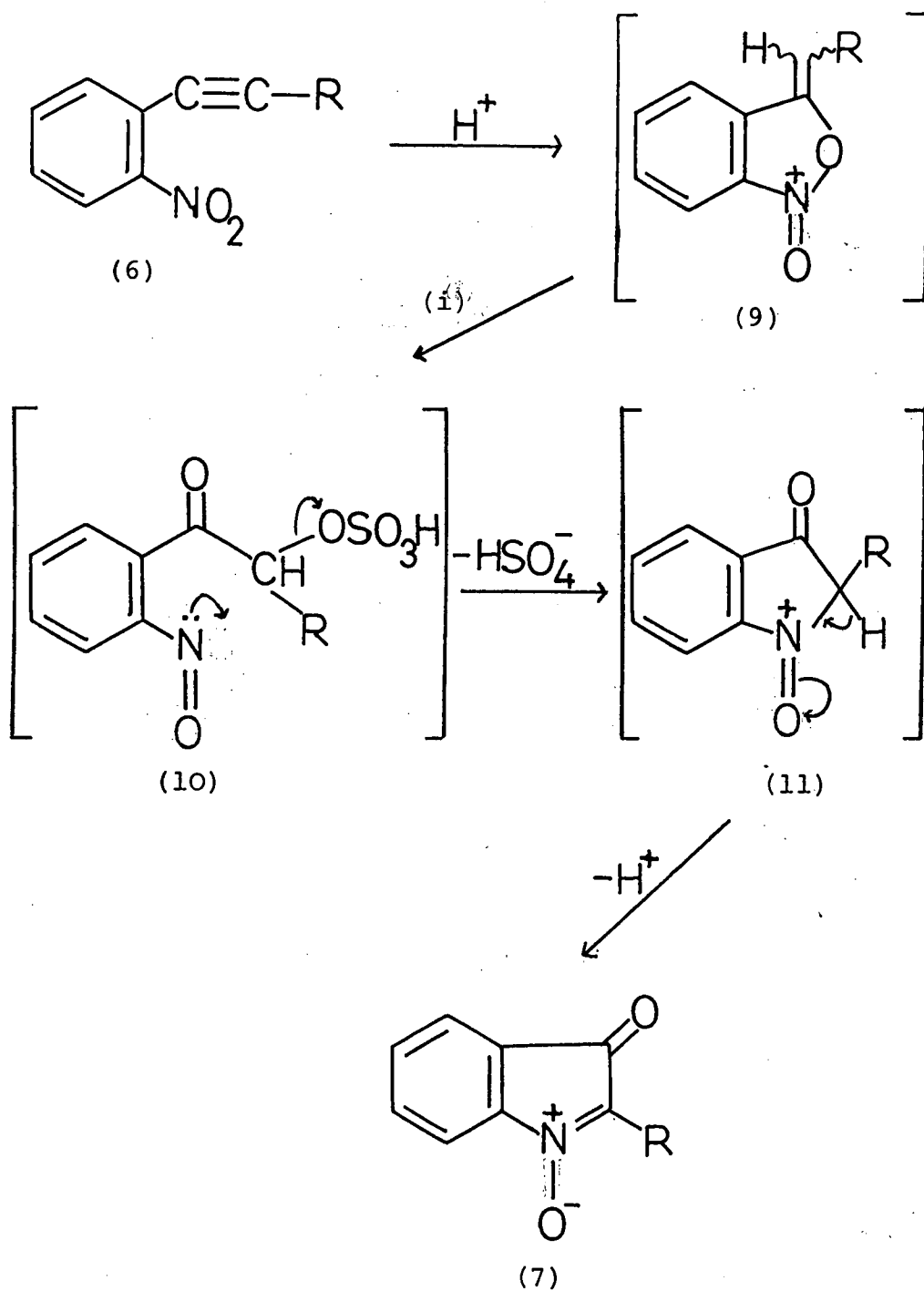
isatogen syntheses can be further sub-divided into (i) catalysed processes and (ii) uncatalysed thermal or photochemical processes. Acid-catalysed cyclisation reactions are of limited application for the general synthesis of isatogens due to the low yields of product usually obtained. In contrast, the corresponding base-catalysed and uncatalysed (thermal and photochemical) processes tend to be more efficient and constitute the principal routes to isatogen derivatives.

(i) Catalysed Processes

(a) Acid-Catalysed Cyclisation Reactions

Leading to Isatogen Derivatives

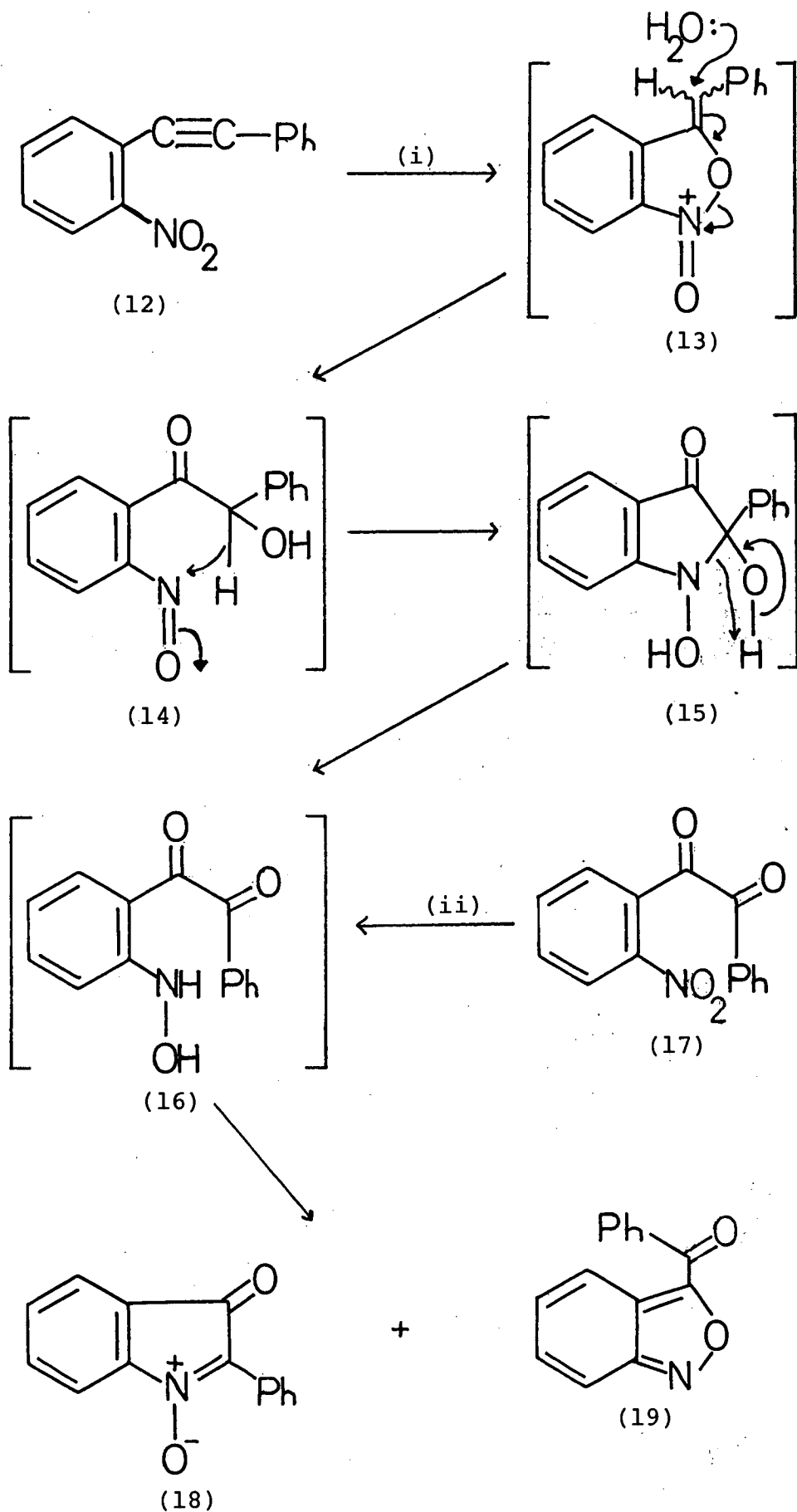
The first isatogens (7a and b) were obtained^{1,2} in good yield by the intramolecular cyclisation (Scheme 2) of 2-nitrophenylacetylenes (6a and 6b) in cold concentrated sulphuric acid. Baeyer⁷ suggested that these unusual heterocyclic reactions involved the preliminary hydration of the acetylenic triple bond to give a keto-intermediate (8) cyclodehydration of which afforded the isatogen. Thus, hydration of the acetylenic ester (6a) would give ethyl 2-nitrobenzoylacetate (8a) and aldol type condensation between the methylene-group and the nitro-group in the latter would then explain the formation of the isatogen derivative (7a). However, this mechanism is ruled out by the finding⁸ that treatment of ethyl 2-nitrobenzoylacetate (8a) results in simple hydrolysis to 2-nitrobenzoylacetic acid rather than cyclisation to the isatogen (7a). Loudon and Tennant⁹



(i), H_2SO_4

\underline{R}
 a; CO_2Et
 b; $2-NO_2C_6H_4C\equiv C$

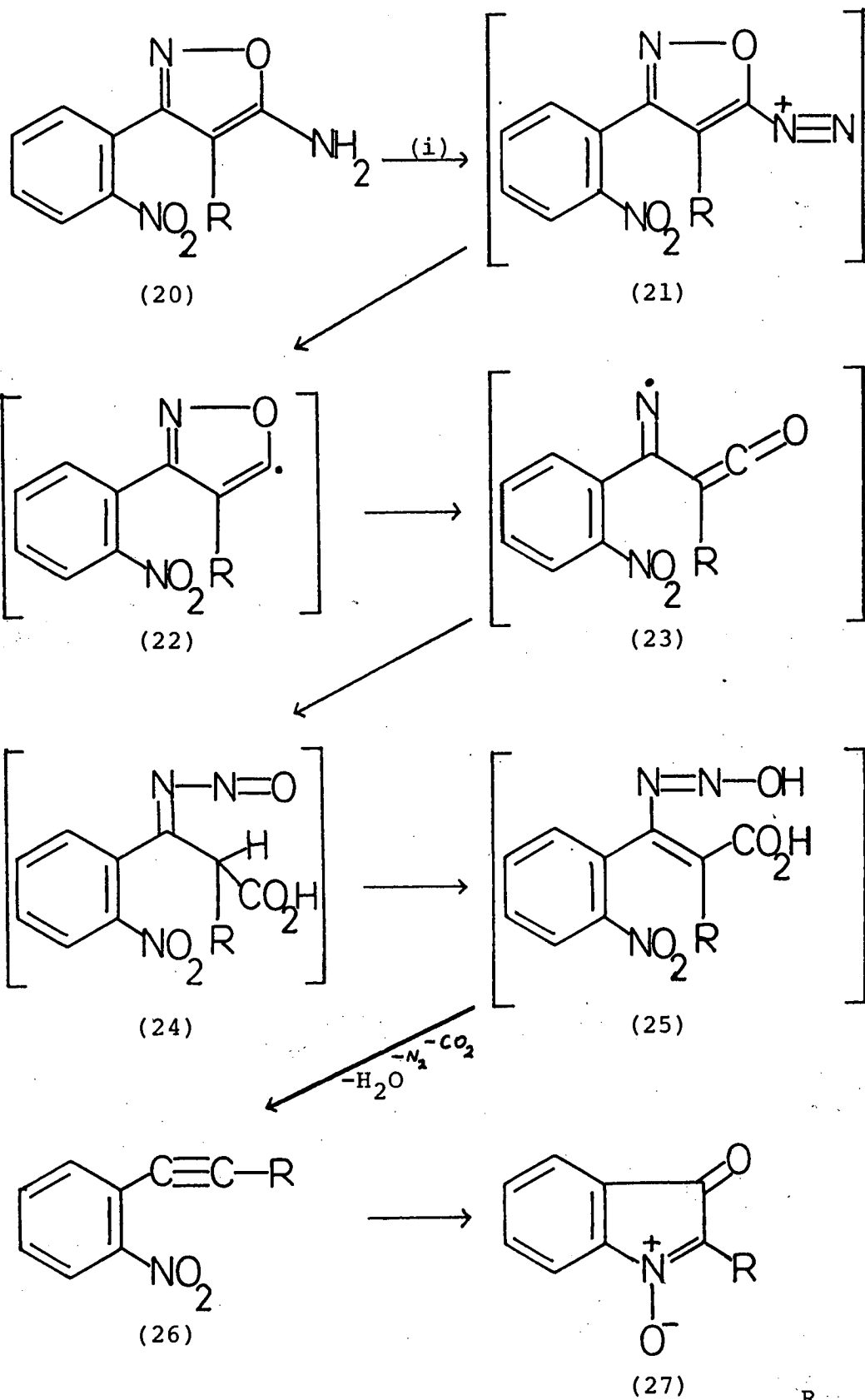
Scheme 3



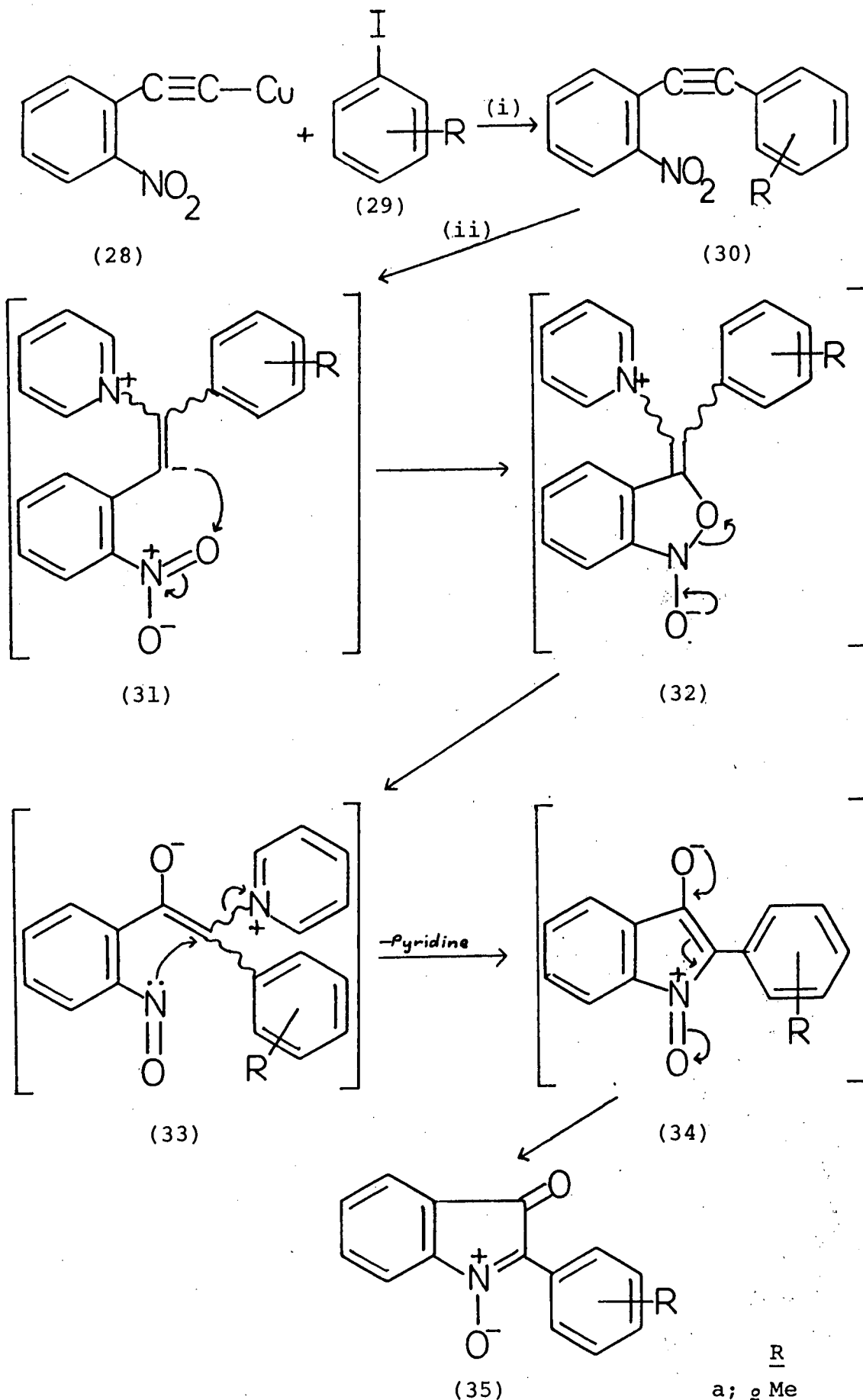
- (i) $2\text{-MeC}_6\text{H}_4\text{SO}_3\text{H}$, toluene, reflux.
(ii) H_2 , Ni .

Scheme 4

have proposed an alternative mechanism for isatogen formation (Scheme 3) involving direct interaction between the ortho-nitro-group and the protonated acetylenic side-chain to give a cyclic intermediate (9) which can react with sulphuric acid to yield a nitroso-compound (10) cyclisation of which would yield the isatogen product [(10) \rightarrow (11) \rightarrow (7)]. A closely related mechanism (Scheme 4) has been proposed by Bakke¹⁰ to account for the toluene-4-sulphonic (tosic) acid-catalysed cyclisation of 1-(2-nitrophenyl)-2-phenylacetylene (2-nitrotolan) (12) to give 2-phenylisatogen (18) and 3-benzoyl-2,1-benzisoxazole (3-benzoylanthranil) (19) both in low yield. These products are explained¹⁰ (Scheme 4) by conversion of the acetylene derivative (12) via the intermediates (13), (14) and (15) into 2-hydroxyaminobenzil (16) which can cyclise through either of the carbonyl groups in the side-chain to afford the observed products (18) and (19). The involvement of 2-hydroxyaminobenzil (16) in the formation of 2-phenylisatogen (18) is supported by the isolation of this compound as a product of the catalytic hydrogenation¹¹ of 2-nitrobenzil (17). 2-Hydroxyaminobenzil (16) is an obvious intermediate in the latter transformation though curiously none of the 2,1-benzisoxazole derivative (19) appears to be formed under catalytic hydrogenation conditions.



Scheme 5



\underline{R}
 a; CH_3
 b; CH_2MeO
 c; CH_2NO_2
 d; $\text{CH}_2\text{CO}_2\text{Et}$

(i) pyridine, reflux
 (ii) pyridine, $h\nu$

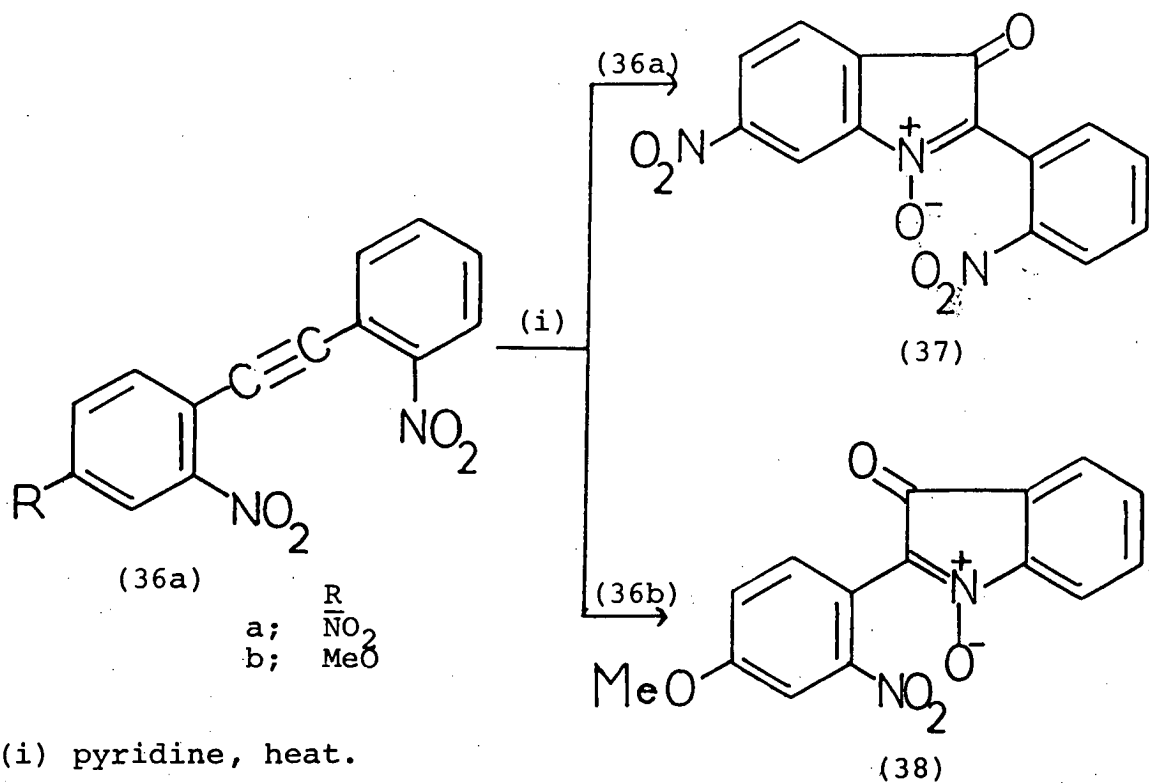
Scheme 6

Recent studies¹² (Scheme 5) have shown that isatogen derivatives (27a and 27b) are formed in low yield as the end-products of the diazotisation reactions of 5-amino-3-(2-nitrophenyl)isoxazole derivatives (20a and 20b). The behaviour of simpler 5-aminoisoxazoles¹² supports a course for these complex reactions (Scheme 5) involving the conversion of the 5-amino-3-(2-nitrophenyl)isoxazoles (20a and 20b) into the corresponding 2-nitrophenylacetylenes (26a and 26b) then in situ acid-catalysed cyclisation of the latter to the isatogen products (27a and 27b).

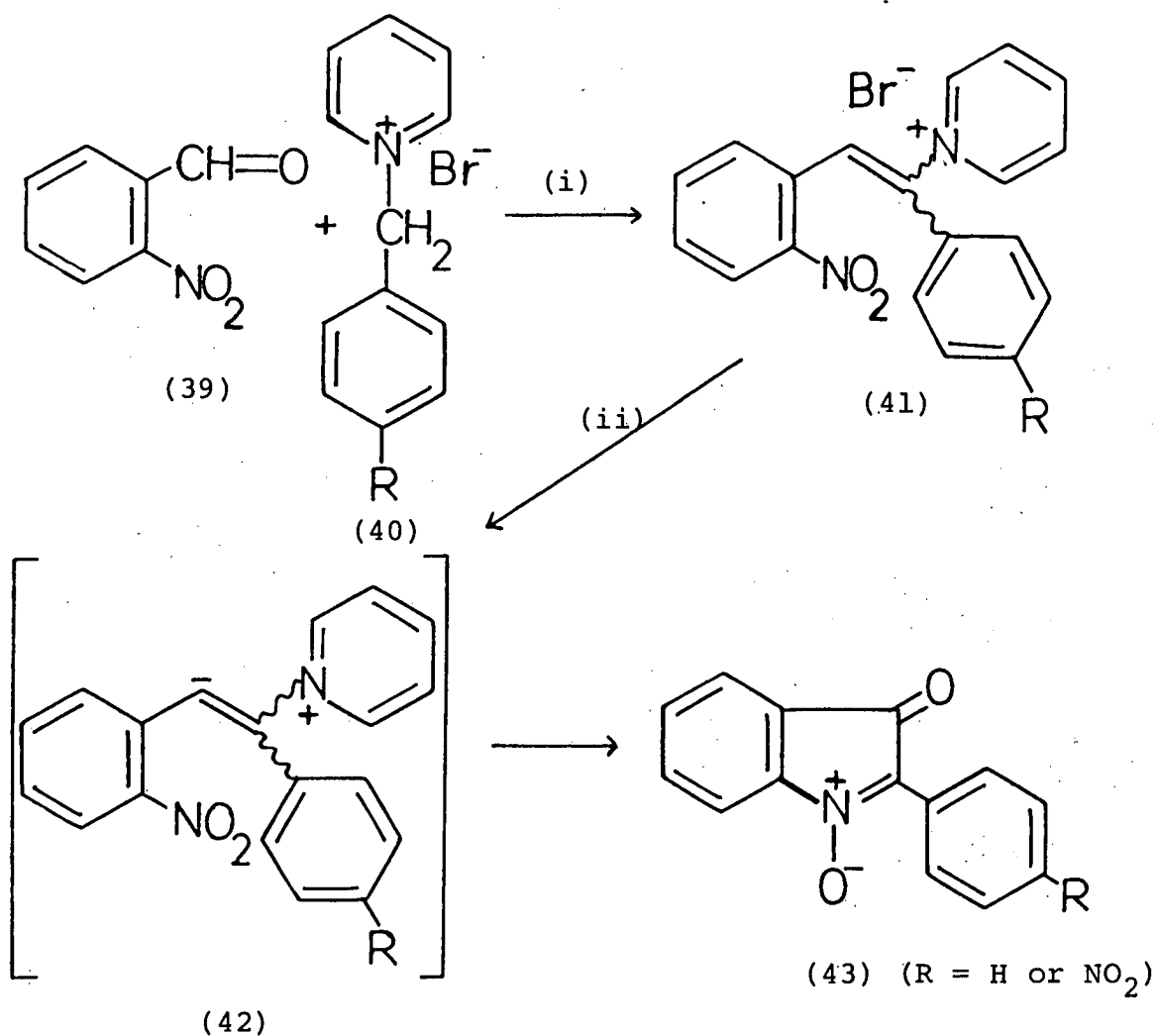
(b) Base Catalysed Cyclisation Reactions

Leading to Isatogen Derivatives

Probably the most straightforward route to isatogen derivatives (Scheme 6) involves the pyridine catalysed cyclisation of 1-aryl-2-nitrophenylacetylenes (2-nitrotolans) (30) to 2-arylisatogens (35).¹³ The general application of this type of isatogen synthesis depends on the general accessibility of the 2-nitrotolan starting-materials (30). These compounds are obtained¹³ in high yield (ca. 80-90%) by heating an appropriate iodobenzene derivative (29) in pyridine with copper(I) 2-nitrophenylacetylde (28) which is readily prepared from 2-nitrophenylacetylene (28; H for Cu) in turn accessible by the decarboxylation of 2-nitrophenylpropionic acid (28; CO_2H for Cu). In the case of meta and para-substituted compounds (30) the conditions of their formation (Scheme 6) tend to result in their



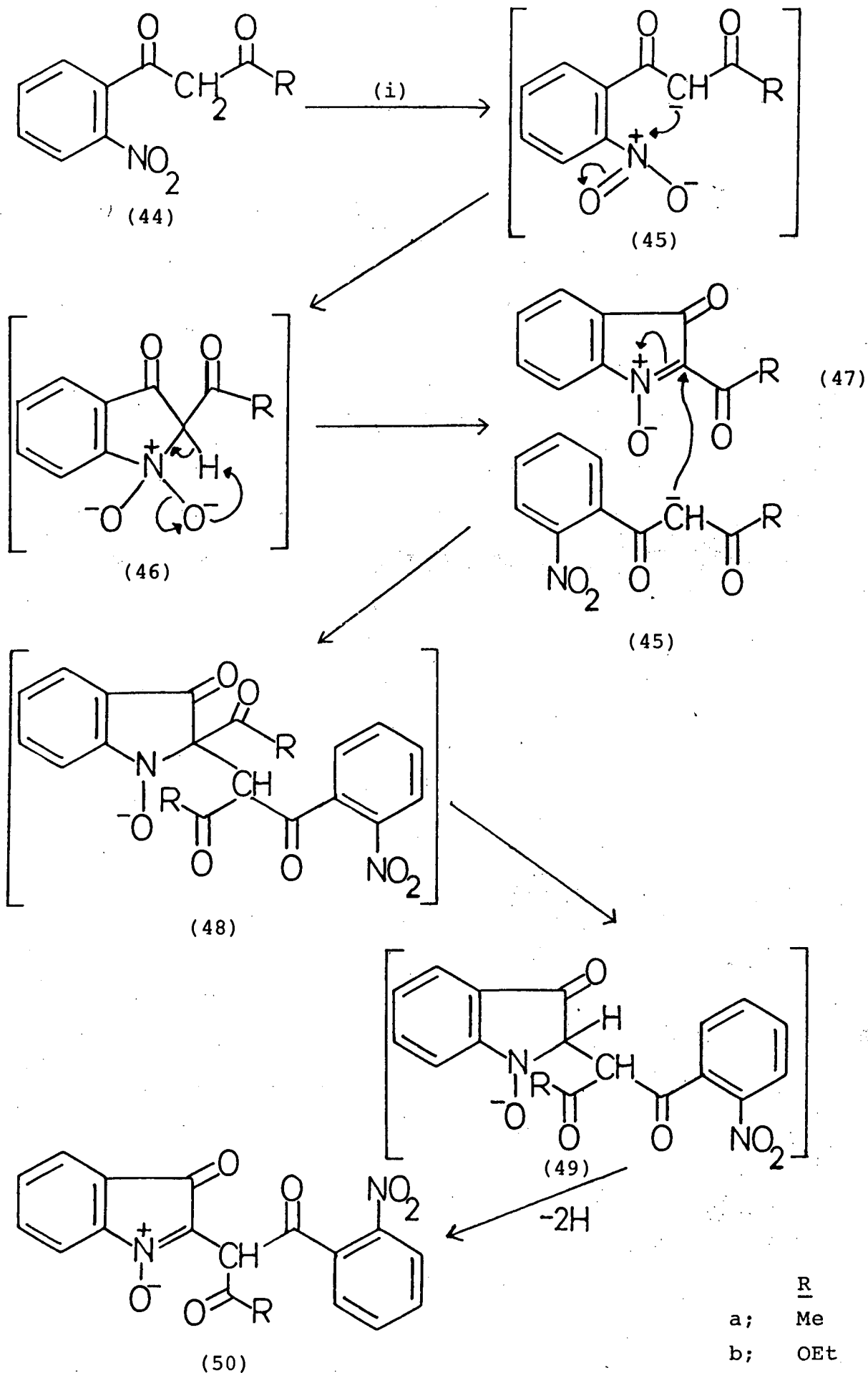
Scheme 7



Scheme 8

spontaneous cyclisation to isatogen derivatives (35). Only in the case of ortho-substituted compounds (30) are the 2-nitrotolan derivatives readily isolated. In these cases subsequent isatogen formation is achieved by heating or irradiating in pyridine solution.

The ease of pyridine-catalysed cyclisation of 2-nitrotolan derivatives to isatogens is markedly influenced by the electronic effect of attached substituents (Scheme 7).¹³ Thus the pyridine-catalysed cyclisation of the 2,2'-dinitrotolan derivative (36a) involves the ortho-nitro-group in the dinitrophenyl ring rather than that in the mono nitrated ring and leads exclusively to the isatogen derivative (37) with no evidence for the formation of the alternative cyclisation product 2-(2',4'-dinitrophenyl)isatogen. Conversely, the pyridine-catalysed cyclisation of the methoxy-substituted 2,2'-dinitrotolan (36b) involves the ortho-nitro-group in the non-methoxylated ring and leads exclusively to the isatogen derivative (38). These results imply that cyclisation is facilitated by electron-withdrawing groups para to the acetylenic side-chain in the 2-nitrotolan and inhibited by electron-donating groups. These substituent effects are consistent with the mechanism (Scheme 6) proposed by Huisgen¹⁴ to account for the pyridine-catalysed cyclisation of 2-nitrotolans (30) to isatogens (35). The key step in this mechanism is the addition of pyridine to the acetylenic triple bond to afford a betaine-type intermediate (31) capable of conversion in several steps through the

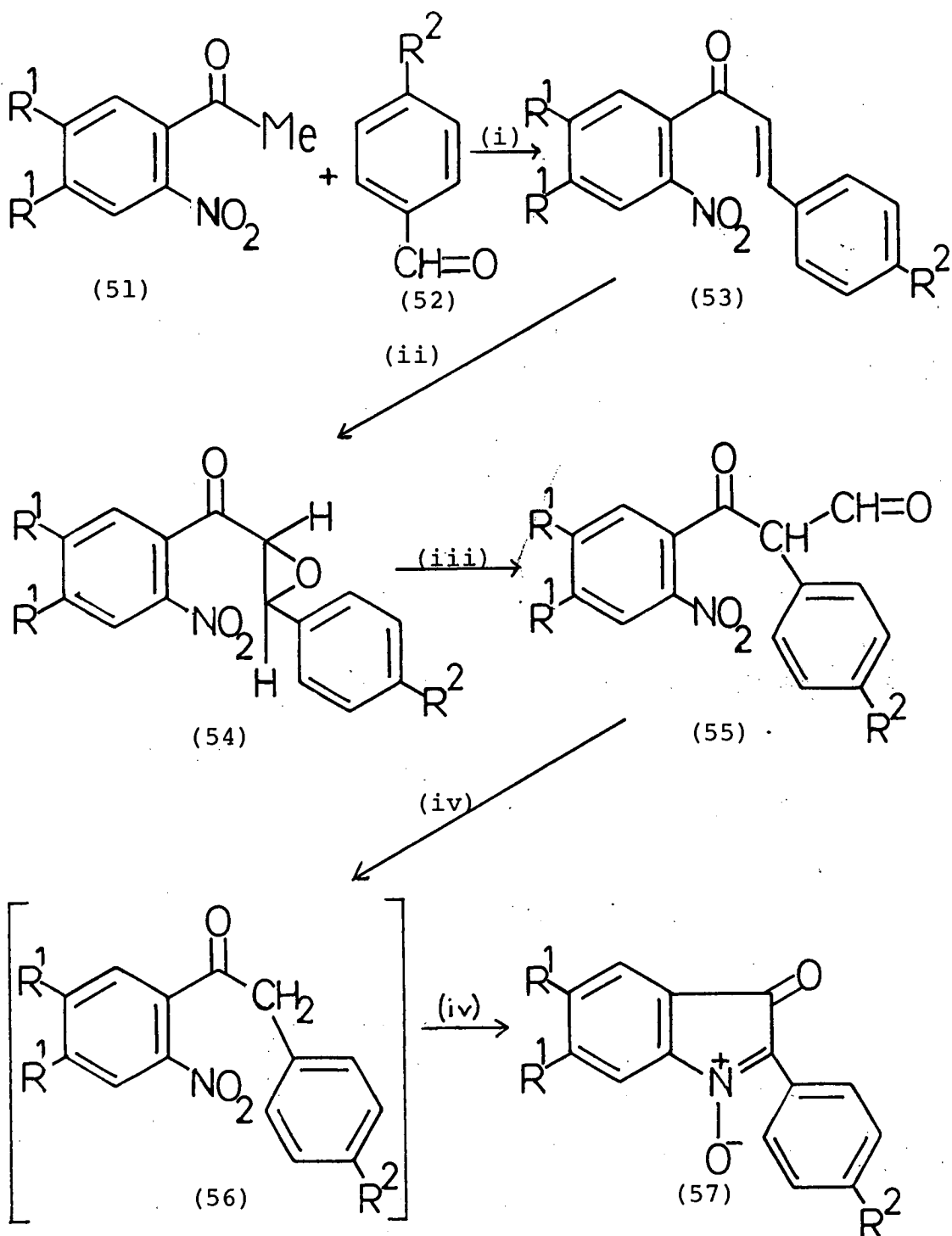


(i) NaHCO_3 , H_2O , room temp.

nitrosobenzene intermediate (33) into the observed isatogen product (35) as outlined in Scheme 6. Electron-withdrawing groups para to the negatively charged carbon atom in the betaine (31) will tend to stabilise it whereas para electron-donating groups will tend to be destabilising, thus accounting for the observed substituent effects.

In processes (Scheme 8) which are probably closely related mechanistically to the pyridine-catalysed cyclisation reactions of 2-nitrotolans already discussed, N-(2-nitrostyryl)pyridinium salts (41) [readily accessible by the acetic anhydride catalysed condensation of 2-nitrobenzaldehyde (39) with N-benzylpyridinium bromides (40)] undergo base-catalysed cyclisation to afford high yields of the corresponding isatogen derivatives (43).^{15,16} These transformations can be explained¹⁵ by the intermediate formation and cyclisation (see Scheme 6) of pyridinium betaines (42).

Isatogen derivatives (50a and b) are also end-products (Scheme 9) of the prolonged treatment of 2-nitrobenzoylacetone (44a) or ethyl 2-nitrobenzoylacetate (44b) with aqueous sodium hydrogen carbonate at room temperature.¹⁷ The isatogen derivative (50b) is also formed in the pyridine-catalysed condensation of 2-carbethoxyisatogen (47b) with ethyl 2-nitrobenzoylacetate (45b). Formation of the isatogen derivatives (50a and b) is therefore readily explained (Scheme 9) in terms of base-catalysed cyclisation of the β -dicarbonyl compounds (44a and b) to the



(i) NaOH, EtOH, H₂O, room temp.

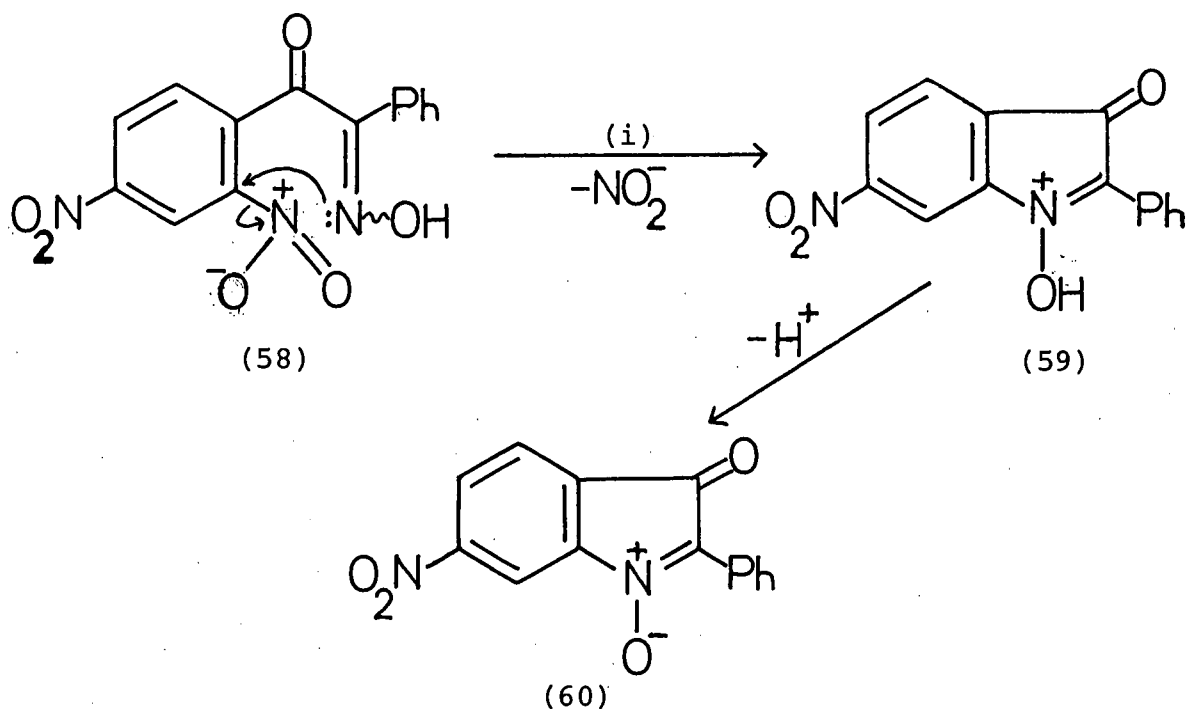
(ii) H₂O₂, NaOH, room temp.

(iii) BF₃-Et₂O, benzene, heat.

(iv) NaOAc, EtOH, H₂O, heat.

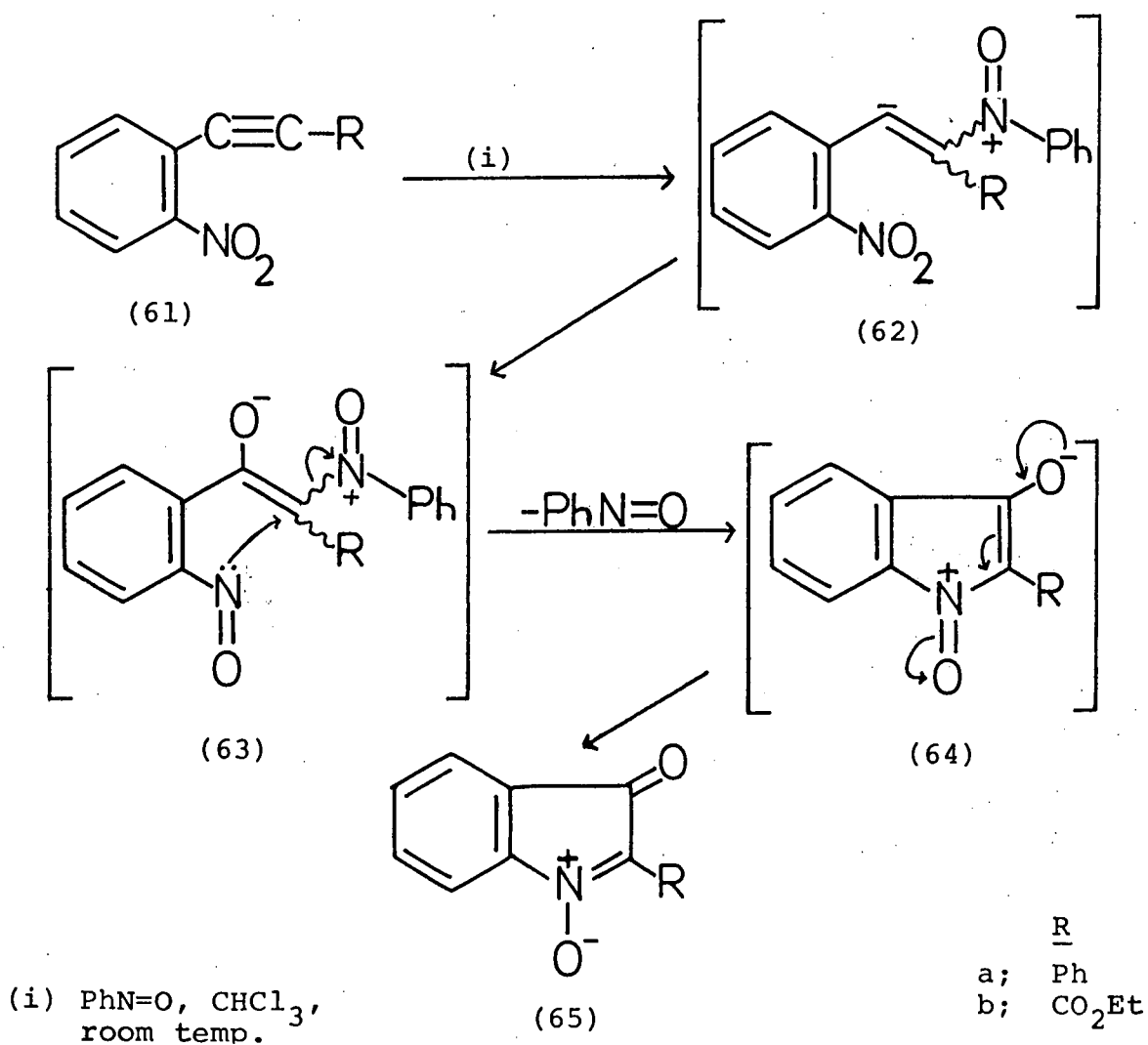
(R¹ = H or OMe; R² = H or Cl).

Scheme 10



(i) NaOEt, EtOH, reflux

Scheme 11

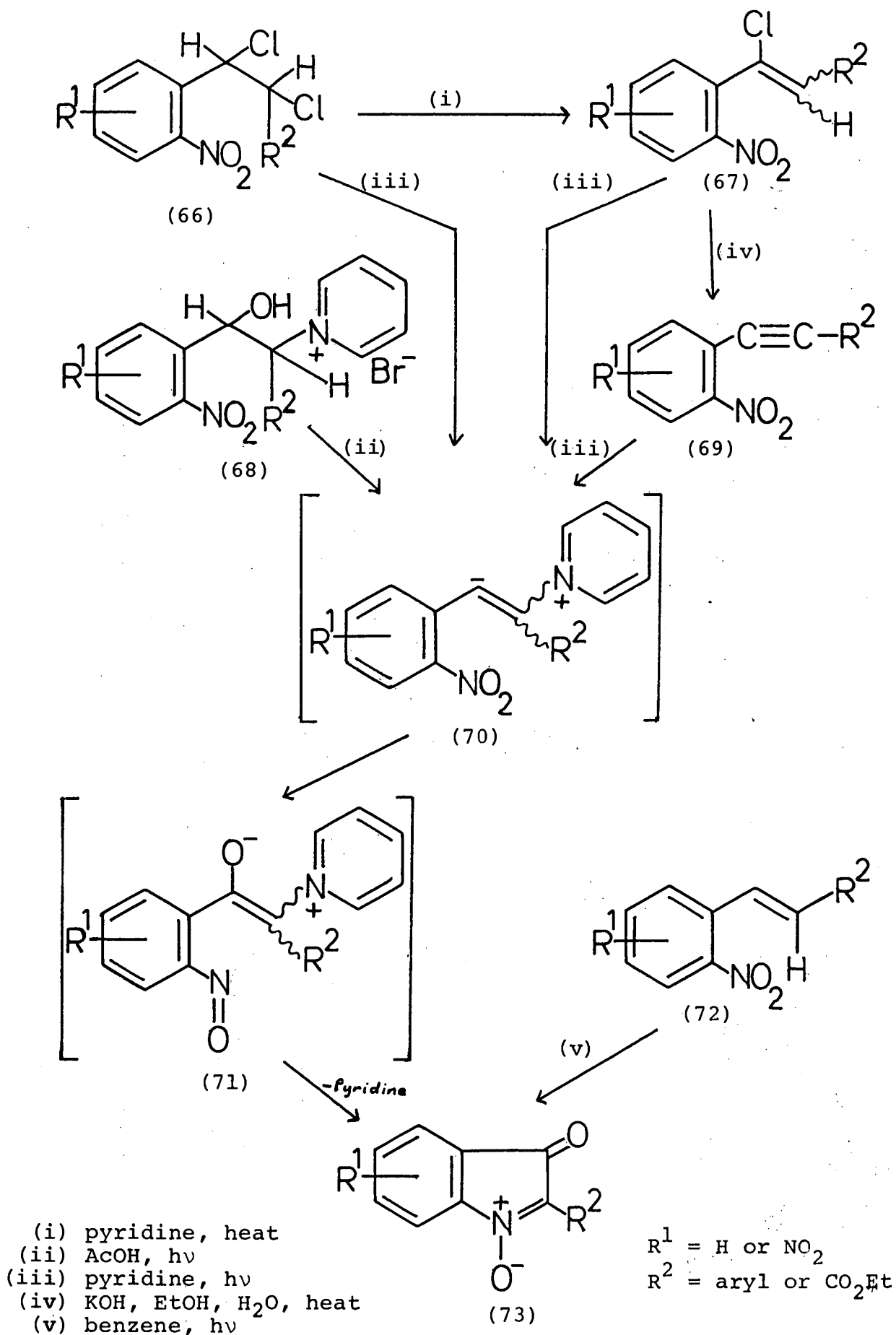


Scheme 12

corresponding 2-acylisatogens (47a and b). These compounds then undergo in situ nucleophilic addition with the carbanion derivatives (45) to give, after deacylation, intermediate adducts (49) in situ oxidation of which accounts for the formation of the isatogens (50a and b).

An elegant general synthesis (Scheme 10) of 2-aryl-isatogens (57) involving the sodium acetate catalysed cyclisation of 1-(2-nitroaryl)-2-arylethanones (56) has recently been described by Kamath and Kulkarni.¹⁸ The ketones (56) required as starting-materials for this isatogen synthesis are obtained in several steps (Scheme 10) from readily accessible arylidene 2-nitroacetophenones (53) via the formyl derivatives (55). Hydrolysis of the latter with aqueous ethanolic sodium acetate affords the ketones (56) which can be converted with or without isolation into the isatogen derivatives (57) in good yield.

In all of the previously discussed base-catalysed cyclisations leading to isatogen derivatives a nitro-group has provided the nitrogen atom of the ultimate isatogen product. In contrast (Scheme 11), the sodium ethoxide catalysed cyclisation¹⁹ of 2,4-dinitrobenzil monoxime (58) to 6-nitro-2-phenylisatogen (60) involves the intramolecular nucleophilic displacement of the ortho-nitro-group by the oxime function and hence the incorporation of the nitrogen-atom of the latter in the fused pyrrole ring. This type of isatogen synthesis does not appear to have been generally exploited, presumably because of the relative inaccessibility of the nitrobenzil monoxime starting-materials.



Scheme 13

(ii) Uncatalysed Processes

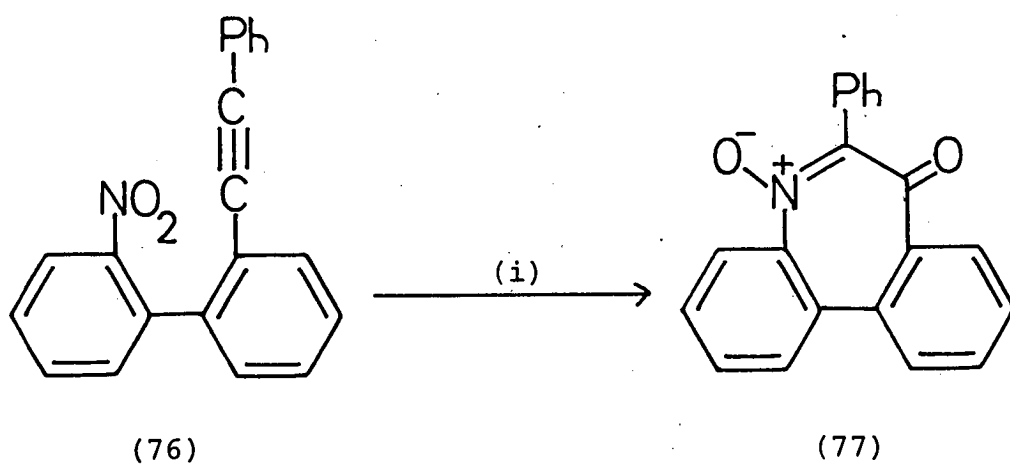
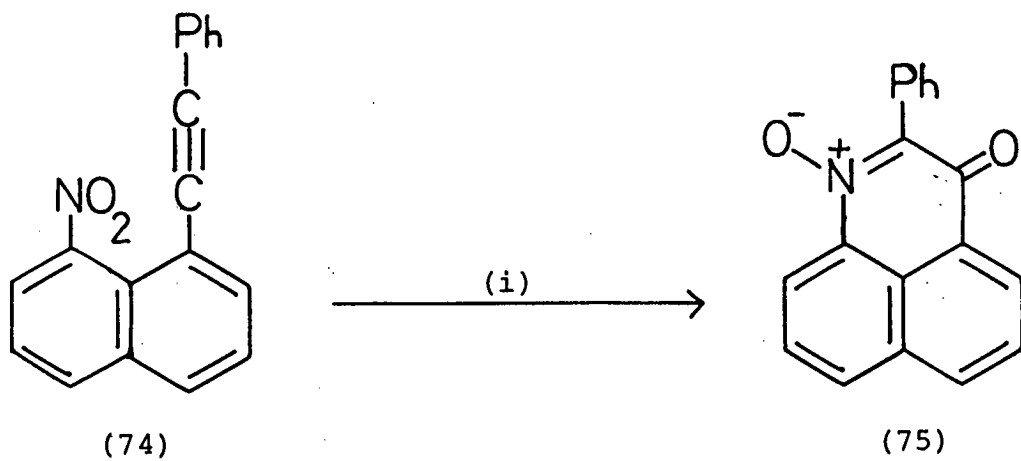
(a) Thermal Cyclisation Reactions Leading to Isatogen Derivatives

Alessandri²⁰ and later Ruggli and his co-workers²¹ showed (Scheme 12) that isatogen derivatives (65a and b) are formed in good yield when the corresponding 2-nitrophenylacetylenes (61a and b) are allowed to react over several days in the dark with nitrosobenzene in chloroform. These interesting transformations are classified as thermal processes purely for convenience though their mechanism is unknown. Patterson²² has suggested (Scheme 12) that the role of the nitrosobenzene is to react with the 2-nitrophenylacetylene derivative (61) to form an intermediate betaine (62), akin to that proposed by Huisgen¹⁴ to account for the pyridine-catalysed cyclisations of 2-nitrophenylacetylene derivatives to isatogens (see Scheme 6 before) and similarly convertible (Scheme 12) into the observed isatogen products (65).

Other purely thermally induced cyclisations affording isatogen derivatives are unknown.

(b) Photochemical Cyclisation Reactions
Leading to Isatogen Derivatives

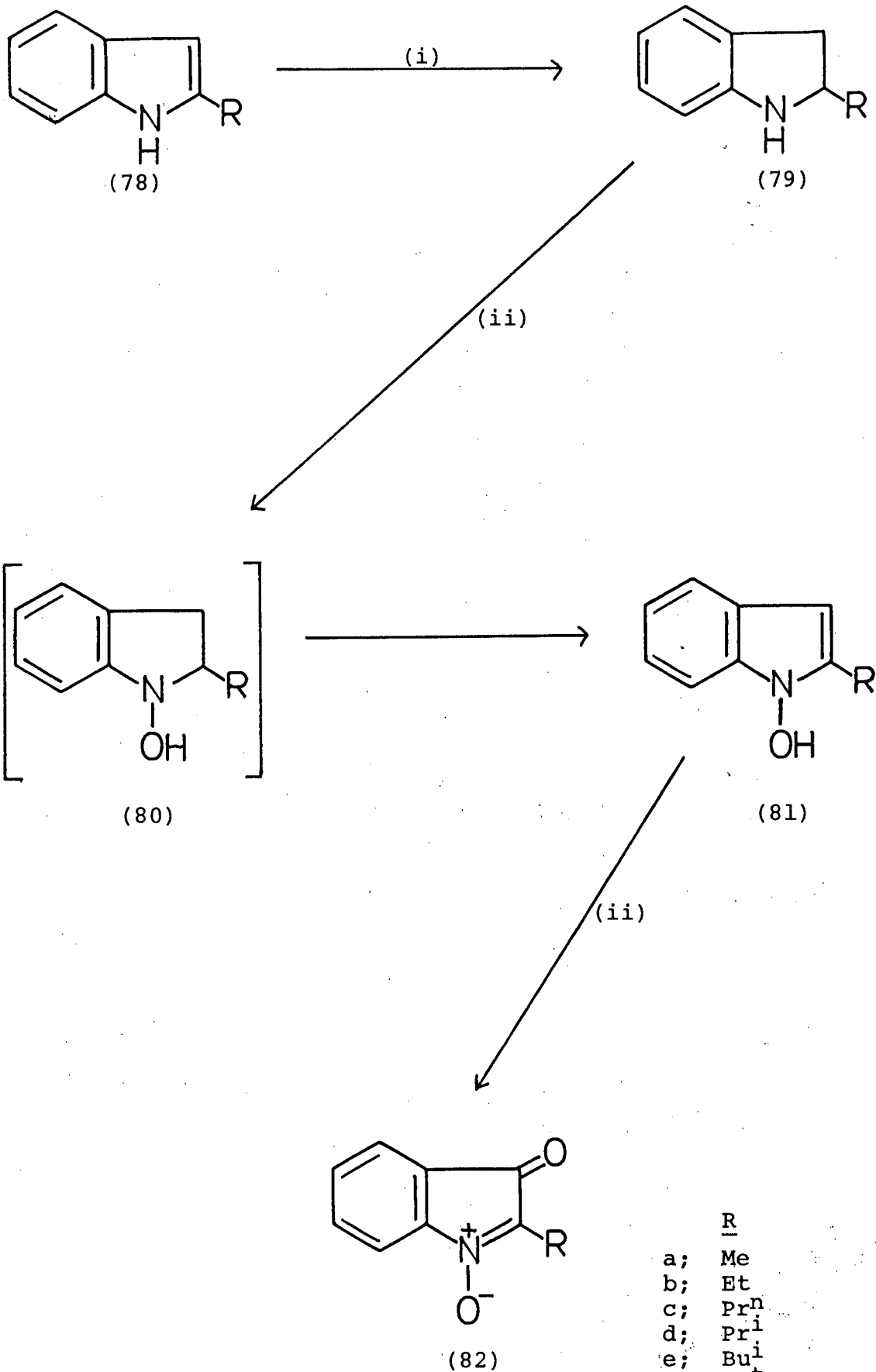
Photocyclisation reactions (Scheme 13) of 2-nitrophenylacetylenes and 2-nitrostilbene derivatives provide perhaps the most successful and widely used methods of isatogen synthesis. Thus, irradiation of pyridine



(i) benzene, $h\nu$

Scheme 14

solutions of 2-nitro phenylacetylenes (69) or the derived 2-nitrostilbene dichlorides (66) or monochlorides (67) with sunlight or ultraviolet light affords moderate to excellent yields of the corresponding isatogen derivatives (73).^{13,23,24} The detailed mechanisms of these photocyclisation reactions are unknown but they can be rationalised^{5,1} in terms of the intermediate formation (Scheme 13) and subsequent cyclisation of pyridinium betaines (70). Intermediates of this type are also postulated¹⁴ to account for the pyridine-catalysed cyclisations of 2-nitrophenylacetylene derivatives to isatogens (see Scheme 6 before). The involvement of pyridinium betaines (70) as intermediates in the pyridine-promoted photocyclisations [(66) or (67) or (69) → (73)] is supported by the observed²⁵ photochemical conversion of N-hydroxyethyl pyridinium salts (68) into isatogens (73) in acetic acid. However, the closely related photocyclisation reactions (Scheme 14) of the nitronaphthylacetylene (74) and the nitrobiphenylacetylene (76) to the novel heterocyclic N-oxides (75) and (77) reported by Leznoff and Hayward²⁶ demonstrate that photo-interaction of a nitro-group with an acetylenic side-chain can occur directly without the involvement of pyridine. Hence it is possible that a mechanism other than that involving pyridinium betaine intermediates, is operating in the pyridine-promoted photocyclisations [(66) or (67) or (69) → (73)]. An alternative mechanism is also required to account for the formation of the corresponding isatogens (73) when trans 2-nitrostilbene derivatives (72) are irradiated in benzene.²⁷

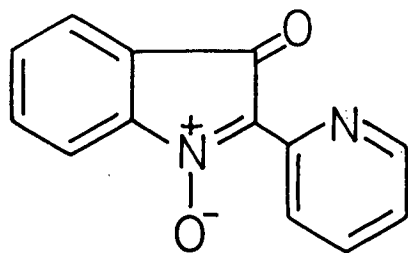


(i) NaBH₃CN, AcOH, room temp.
or 50-60°.

(ii) 3-ClC₆H₄CO₂H, CHCl₃ or Et₂O,
room temp.

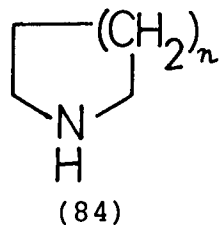
(b) Isatogen Syntheses Based on Oxidative Transformations of Indole Derivatives

The oxidation (Scheme 15) of 2-substituted indolines (79) or of 2-substituted 1-hydroxyindoles (81) provides useful routes^{28,29} to isatogens (82) which complement those based on cyclisation reactions of 2-nitrophenylacetylenes and 2-nitrophenylalkenes (see before). The oxidative methods (Scheme 15) are particularly useful for the synthesis of 2-alkylisatogens (82a-g) which are not available by direct cyclisation procedures. 2-Substituted indoline starting-materials (79) are readily available by the reduction of indoles (78) with sodium cyanoborohydride and are smoothly converted by oxidation with meta-chloro-perbenzoic acid under mild conditions into isatogen derivatives in good yield. These transformations are suggested²⁸ to occur by oxidation of the indolines (79) to N-hydroxyindolines (80) followed by dehydrogenation to 1-hydroxyindoles (81) then oxidation of the latter to the corresponding isatogens (82). The initial N-hydroxylation of the indolines (79) to the N-hydroxy derivatives (80) is supported by the known³¹ selective peracid oxidation of secondary amines to secondary hydroxylamines. Correspondingly, 1-hydroxyindoles (81) have been shown²⁹ to be smoothly oxidised by peracid to isatogens (82) in high yield.



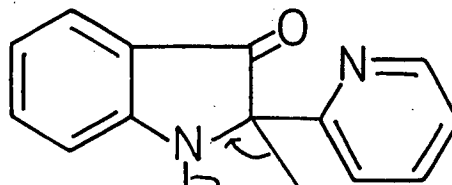
(83)

+



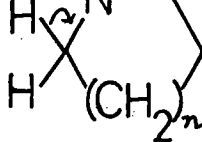
(84)

(i)



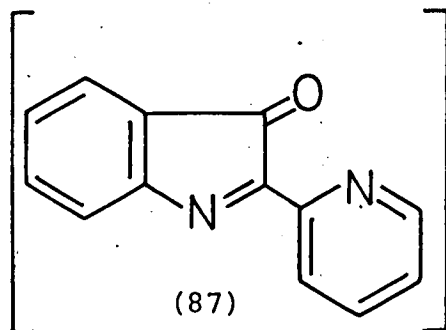
(85)

(ii)



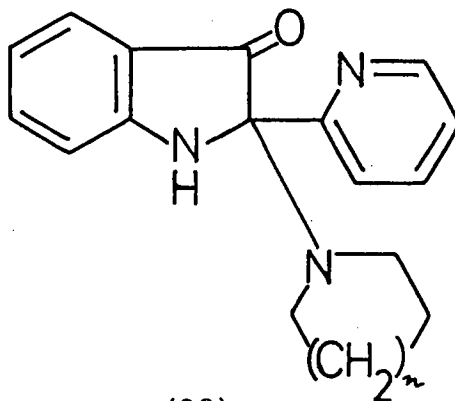
(86)

+



(87)

(84)



(88)

(n = 1 or 2)

- (i) EtOAc, room temp.
(ii) EtOAc, heat.

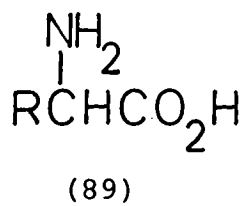
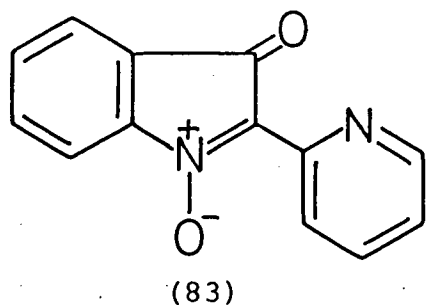
The Reactivity of Isatogens

Isatogens have unique structures which incorporate both a carbonyl group and a nitron moiety ($\text{C}=\text{N}^+-\text{O}^-$) and accordingly they exhibit chemical reactivity typical of nitrones on the one hand and carbonyl compounds on the other. However the chemical behaviour of isatogens tends to be dominated by their nitron-like reactivity.

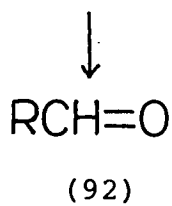
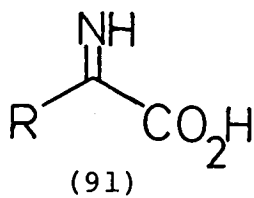
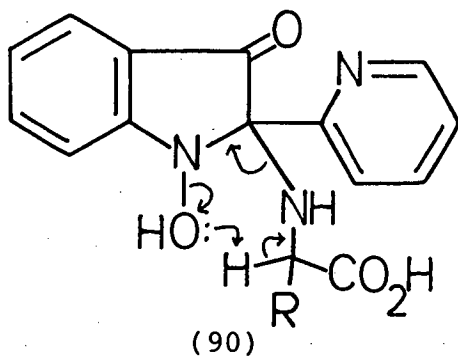
Studies of the chemical reactivity of isatogens have been largely carried out with the most readily obtainable 2-aryl and 2-ethoxycarbonyl derivatives. In the following survey the reactivity of isatogens is discussed under two headings, depending on whether the reaction largely involves the nitron moiety or the carbonyl group respectively.

(a) Reactivity of Isatogens as Nitrones

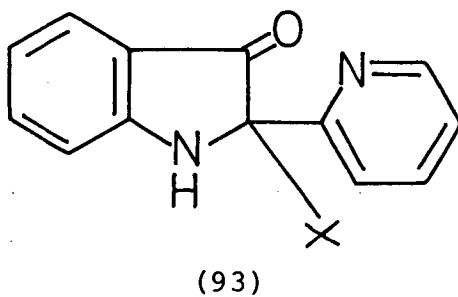
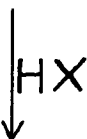
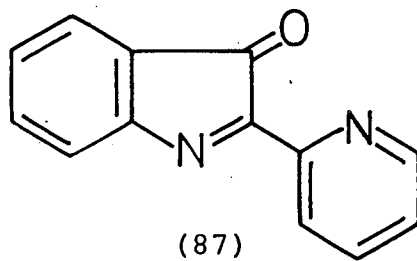
Isatogens, like typical nitrones,⁶ undergo nucleophilic addition and 1,3-dipolar cycloaddition reactions. Typical of the former reactivity are the reactions (Scheme 16) of isatogens with the cyclic secondary amines pyrrolidine (84; $n = 1$) and piperidine (84; $n = 2$). At room temperature 2-(2-pyridyl)isatogen (83) reacts³² with piperidine (84; $n = 2$) in ethyl acetate to afford green crystals of the nucleophilic adduct (85; $n = 2$) which tends to decompose to the isatogen (83) and piperidine (84; $n = 2$) in organic solvents. On the other hand, heating³² the



(i)



+



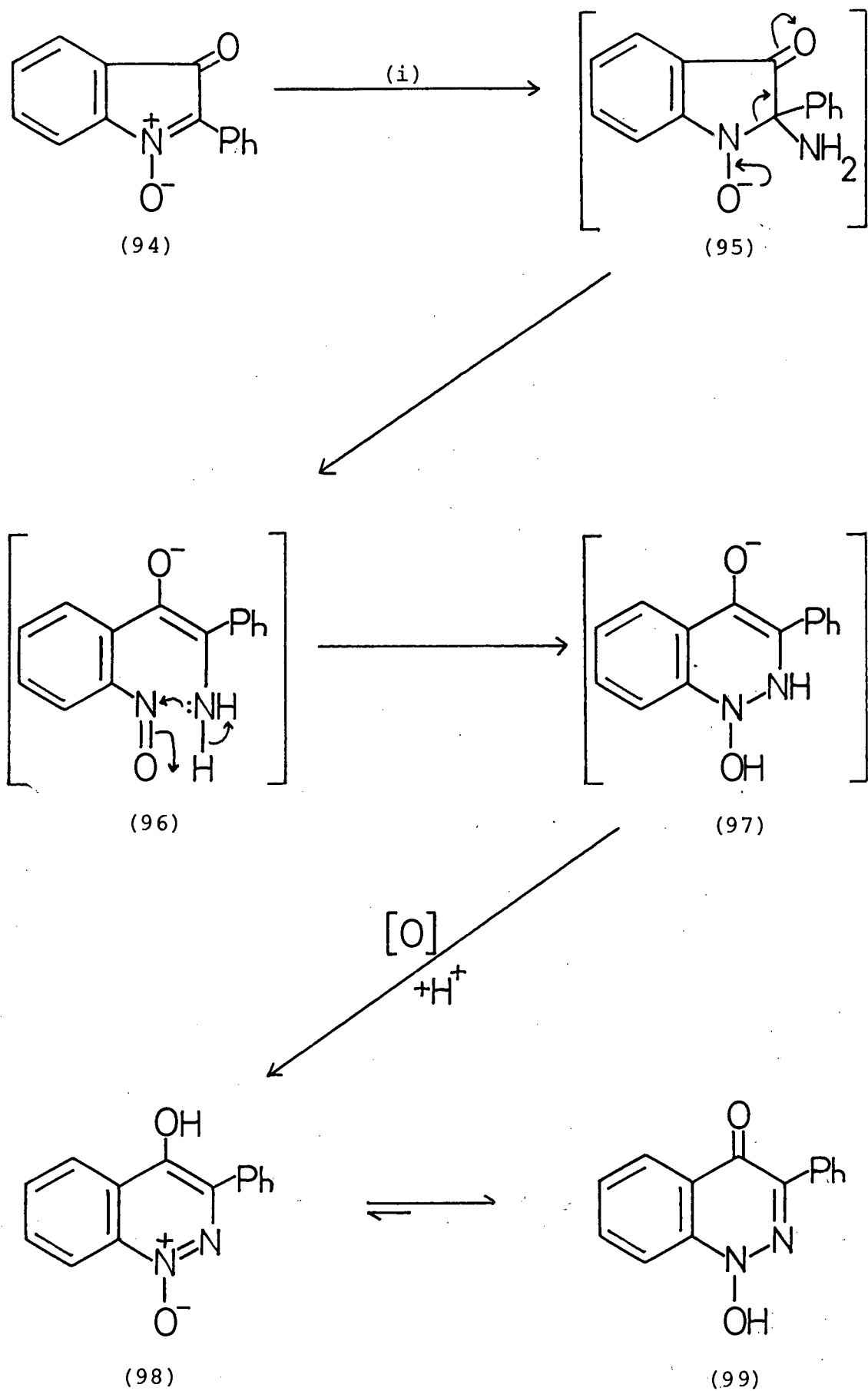
(R = Prⁱ, Buⁱ)

(i) EtOH, H₂O, N₂, reflux.

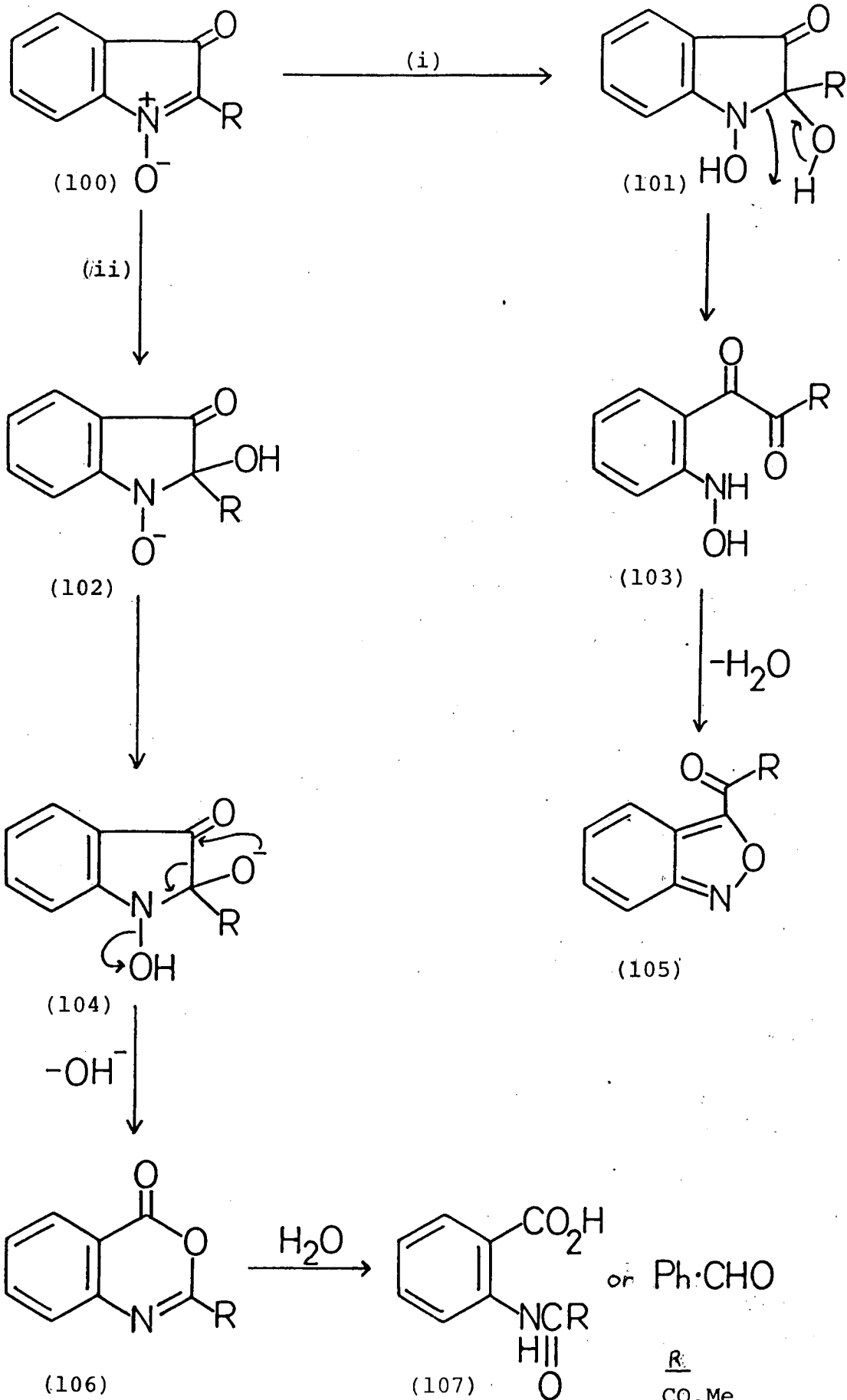
$\overline{\text{X}}$
a; OH
b; OEt
c; NH₂

Scheme 17

isatogen (83) with excess of piperidine (84; $n = 2$) in ethyl acetate affords the yellow indolone derivatives (88; $n = 2$). The transformations [(83) + (84; $n = 2$) \rightarrow (88; $n = 2$)] can be explained (Scheme 16) in terms of the initial formation of the adduct (85; $n = 2$) which breaks down as shown to afford the Δ' -pyrroline (86; $n = 2$) and the indolone (87). Nucleophilic addition of piperidine (84; $n = 2$) at the reactive 2-position in the indolone (87) then accounts for the formation of the indolone adduct (88; $n = 2$). This mechanism is supported by the isolation³² of a by-product, tentatively identified as the pyrroline (86; $n = 1$), in the reaction of the isatogen (83) with pyrrolidine (84; $n = 1$) to afford the indolone adduct (88; $n = 1$). The involvement of the indolone (87) in the reactions of 2-(2-pyridyl)isatogen (83) with amines is further substantiated (Scheme 17) by the reactions with α -amino acids (89).³³ When the isatogen (83) is heated with the amino acids (89) in aqueous ethanol under nitrogen the products in addition to ammonia and the corresponding aldehydes (92) are the indolone adducts (93a-c). Clearly, the products (93a and b) arise by the trapping of the indolone (87) in the aqueous ethanolic medium while the adduct (93c) is derived by the reaction of the indolone (87) with ammonia detectable as a by-product of the reaction. The formation of ammonia and the corresponding aldehydes (92) as by-products supports a mechanism (Scheme 17) for the reactions of the isatogen (83) with the amino acids (89) involving the formation of the intermediate adducts (90)



(i) NH_3 , EtOH, 140-145°

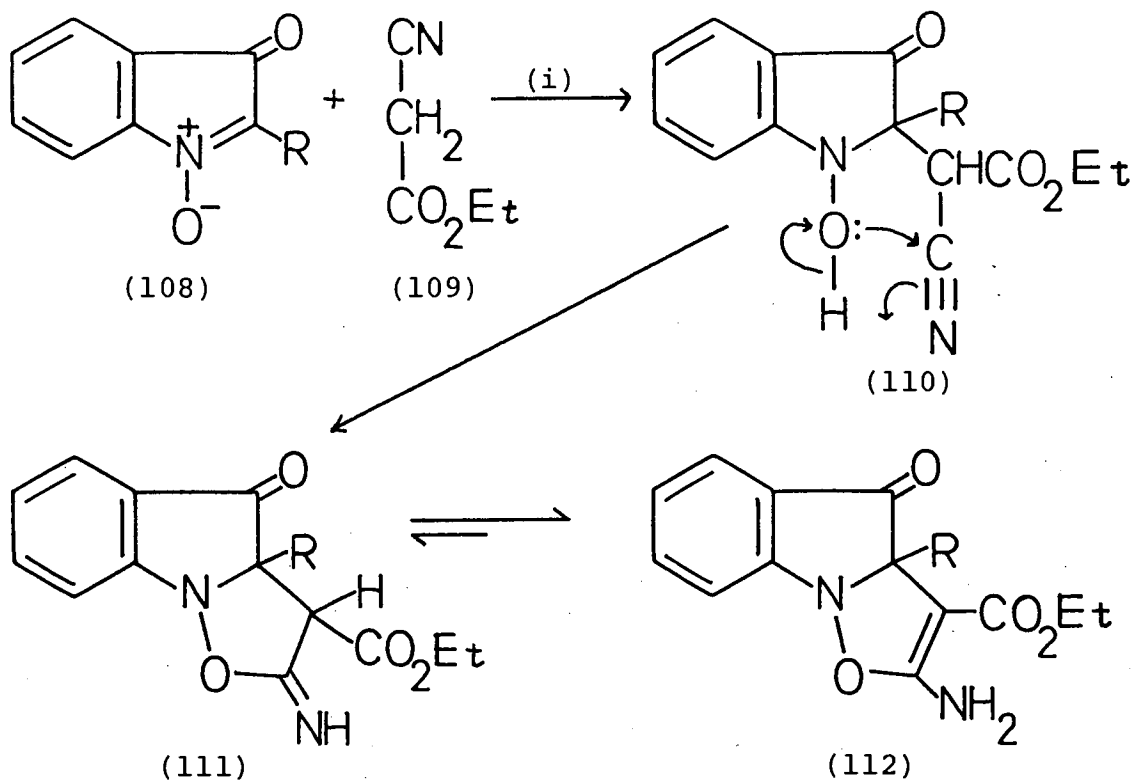


(i) H_2SO_4 , MeOH, 100° .
 (ii) 5M NaOH, EtOH, room temp.

subsequent breakdown of which would afford the indolone (87) and the imino-acids (91). Hydrolytic decomposition of the latter in the aqueous reaction mixture then accounts for the formation of the aldehydes (92) and ammonia.

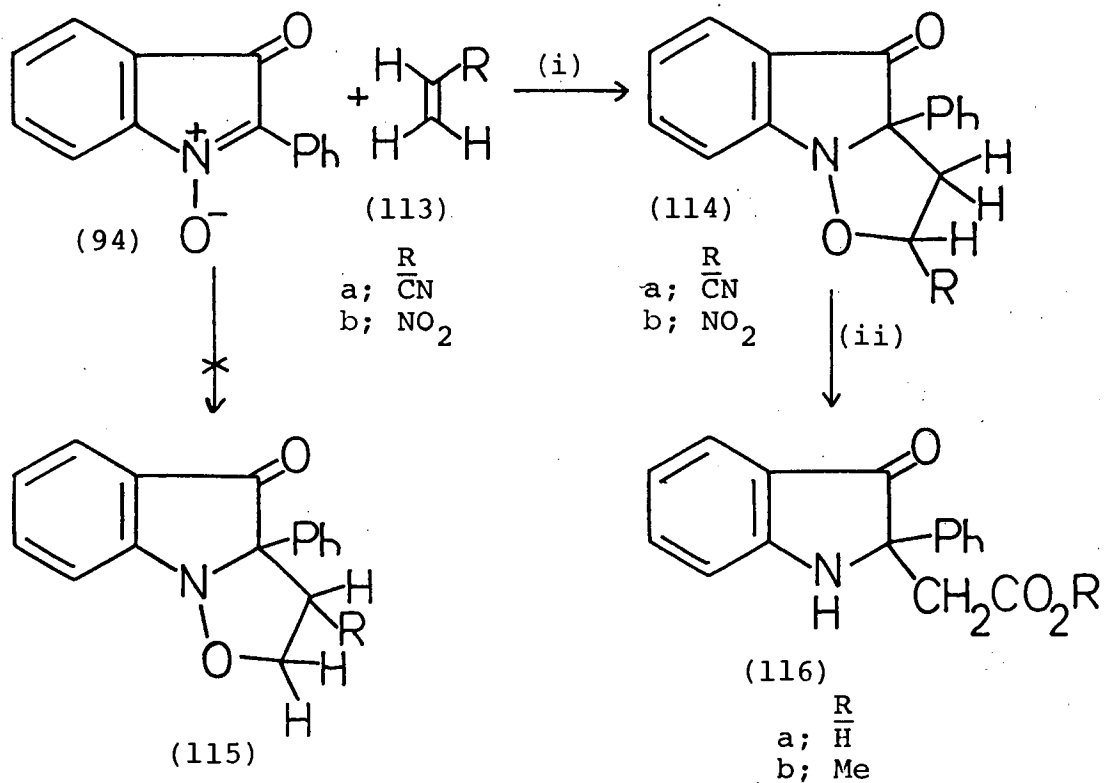
The reaction (Scheme 18) of 2-phenylisatogen (94) with ammonia in ethanol at elevated temperature affords a low yield (26%) of the tautomeric N-hydroxycinnolinone (99).³⁴ This transformation can be explained by a course (Scheme 18) initiated by nucleophilic addition of ammonia at the "reactive" 2-position of the isatogen (94) to give an adduct (95) ring-opening of which would yield the nitroso-intermediate (96). Spontaneous cyclisation of this compound followed by in situ oxidation of the resulting 1,2-dihydrocinnoline (97) then accounts for the N-hydroxycinnolinone end-product (99).

Base- and acid-catalysed hydrolytic rearrangements (Scheme 19) undergone by isatogens (100) also appear to be promoted by initial nucleophilic attack by hydroxide ion or a water molecule at the "reactive" 2-position. Hooper and Wibberley¹⁷ have shown (Scheme 19) that certain isatogen derivatives (100a) react with cold alkali to afford the corresponding benzoxazines (106a) while under more vigorous alkaline conditions^{19,35} the products are N-acyl anthranilic acids (107; R = Ph) or benzaldehyde formed by further hydrolysis. These base-catalysed isatogen transformations



(i) piperidine, EtOH, room temp.

Scheme 20

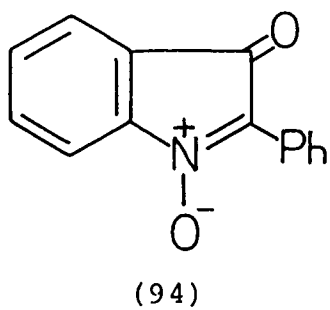


(i) xylene reflux.
(ii) MeOH or NaOH, MeOH, reflux.

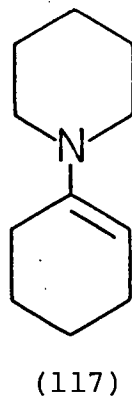
Scheme 21

are suggested¹⁷ to occur by initial nucleophilic attack by hydroxide ion at the 2-position in the isatogens (100) to afford intermediate adducts (102) which give rise to the benzoxazines (106) by proton transfer, then ring-expansion with accompanying expulsion of hydroxide ion [(102) \rightarrow (104) \rightarrow (106)]. In contrast, acid-catalysed transformations of isatogens follow a different pathway (Scheme 19). Thus, heating 2-phenylisatogen (100; R = Ph) with methanolic sulphuric acid converts it into 3-benzoyl-2,1-benzisoxazole (105).³⁶ The formation of this product is readily explained by a course (Scheme 19) effectively involving hydration of the isatogen (100; R = Ph) to the adduct (101; R = Ph), then ring opening to the hydroxyamino-compound (103) followed by recyclisation of the latter to the observed 2,1-benzisoxazole product (105).

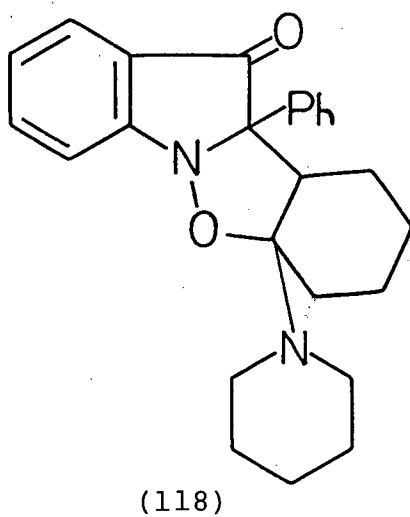
Isatogens are also susceptible to nucleophilic attack at the 2-position by carbanions. Typical of such reactions (Scheme 20) is the piperidine-catalysed condensation of various isatogen derivatives (108) with ethyl cyanoacetate (109) to give high yields of the fused isoxazole products (112).³⁷ These interesting reactions are most readily explained by initial nucleophilic addition of the carbanion derived from ethyl cyanoacetate at the 2-position of the isatogens (108) to afford adducts (110) intramolecular cyclisation of which would give the fused isoxazole products (112).



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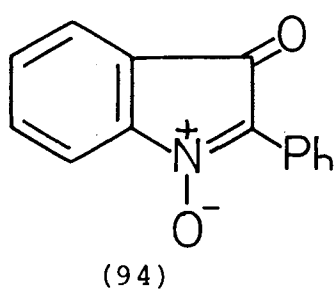


(i)

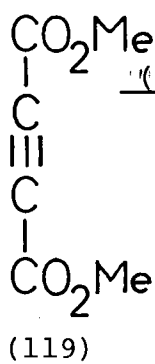


(i) CH_2Cl_2 , heat

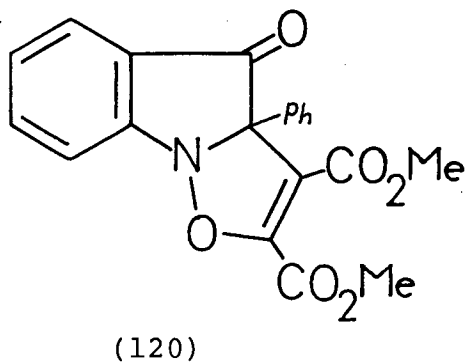
Scheme 22



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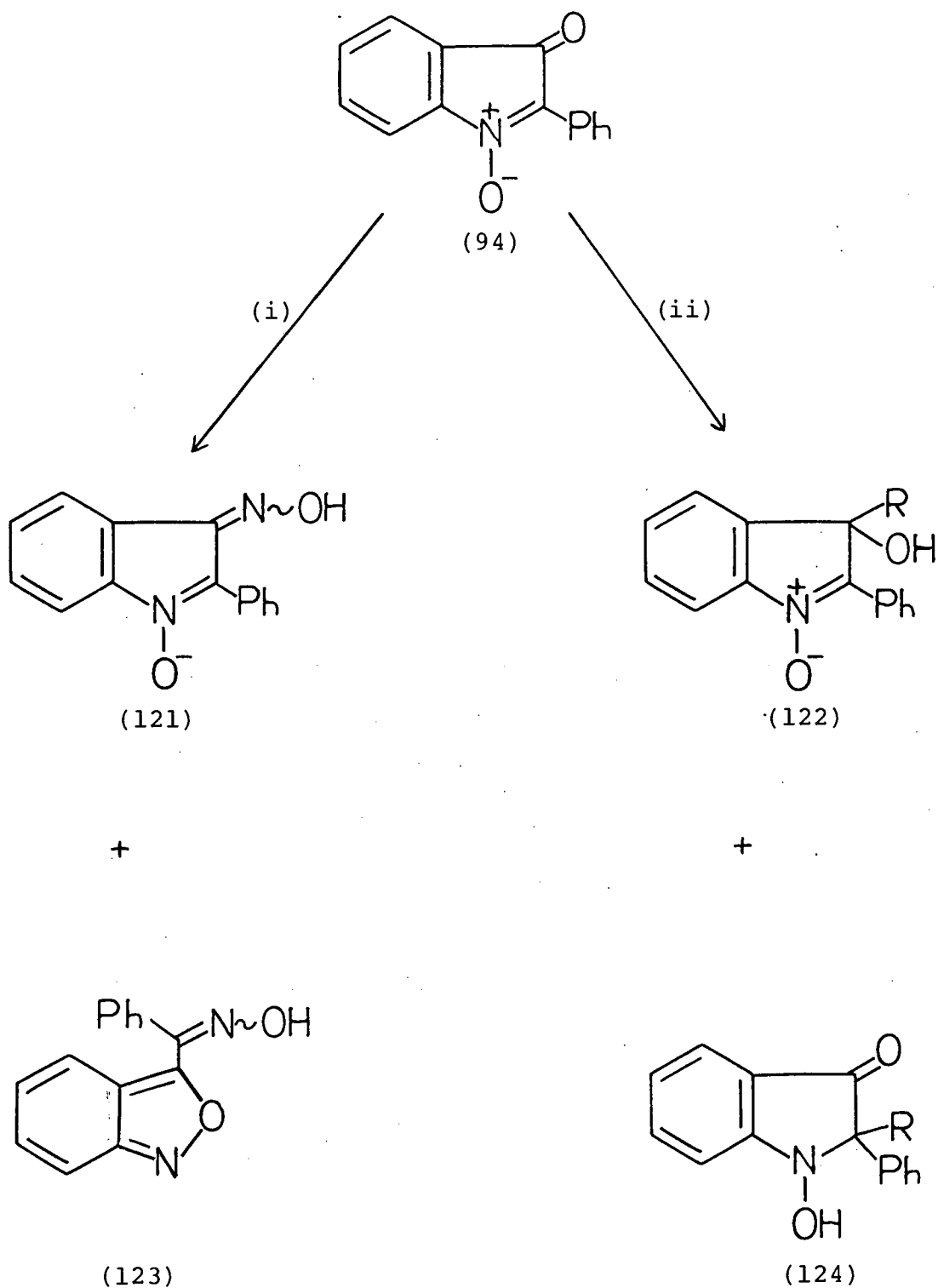
(i)



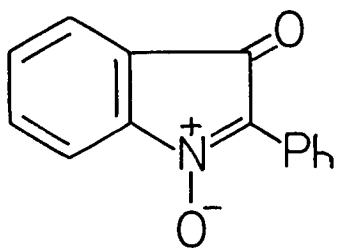
(i) xylene, reflux

Scheme 23

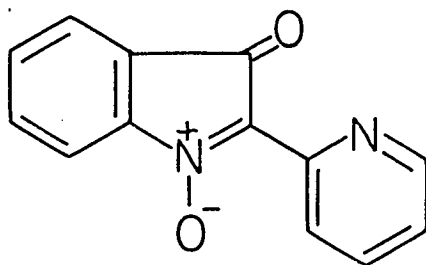
Isatogens like other typical nitrones⁶ participate as 1,3-dipoles in 1,3-dipolar cycloaddition reactions. For example (Scheme 21), heating 2-phenylisatogen (94) with acrylonitrile (113a) or nitroethylene (113b) in xylene affords moderate yields of the cycloadducts (114a and b).³⁸ These structures for the products rather than the alternative orientations (115) follow from their methanolysis or hydrolysis to the ring opened indolinones (116a and b) of established structure.³⁸ The orientations (114) for the cycloadducts of isatogens with electron-poor alkenes is the reverse of that observed³⁹ in analogous cycloaddition reactions of simpler nitrones. The unexpected orientation of the cycloadducts of electron-poor alkenes with isatogens has been attributed to control of the direction of cycloaddition by back electron-donation by the N-oxide⁶ oxygen atom. The dipolar cycloaddition of an isatogen to an electron-rich alkene is illustrated (Scheme 22) by the reaction⁴⁰ of 2-phenylisatogen (94) with the piperidine enamine of cyclohexanone (117) to give the cycloadduct (118). The orientation of this product is in accord with the direction of cycloaddition observed³⁹ in the reactions of simpler nitrones with electron-rich alkenes. The cycloaddition of the nitrone functionality of an isatogen to a carbon-carbon triple bond is illustrated (Scheme 23) by the formation of the cycloadduct (120) when 2-phenylisatogen (94) is heated under reflux with dimethyl acetylenedicarboxylate (119) in xylene.⁴¹



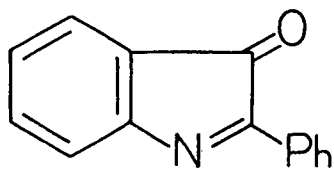
- (i) $\text{NH}_2\text{OH} \cdot \text{HCl}$, EtOH, heat
- (ii) RMgX , ether-dioxane or THF, room temp.
or RLi , benzene, room temp.



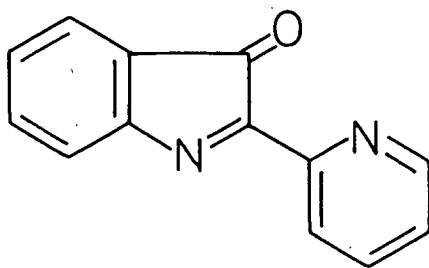
(94)



(125)



(126)



(127)

Scheme 25

(b) Reactivity of Isatogens as Carbonyl Compounds

Reactions of isatogens as carbonyl compounds tend to be complicated by competing reaction at the nitron moiety (Scheme 24). However, 2-phenylisatogen (94) reacts with hydroxylamine in orthodox fashion to afford the oxime (121) together with the oxime of 3-benzoyl-2,1-benzisoxazole (123).³⁶ The latter product presumably arises by rearrangement of 2-phenylisatogen (94) to 3-benzoyl-2,1-benzisoxazole (105; R = Ph) (see page 35 and Scheme 19 before) followed by oximation. Grignard and organolithium reagents react (Scheme 24) with 2-phenylisatogen (94) both at the carbonyl group and at the C-2 position to afford mixtures of the corresponding 3H-indole N-oxides (122) and N-hydroxyindolinones (124).^{42,43}

The Biological Activity of Isatogens

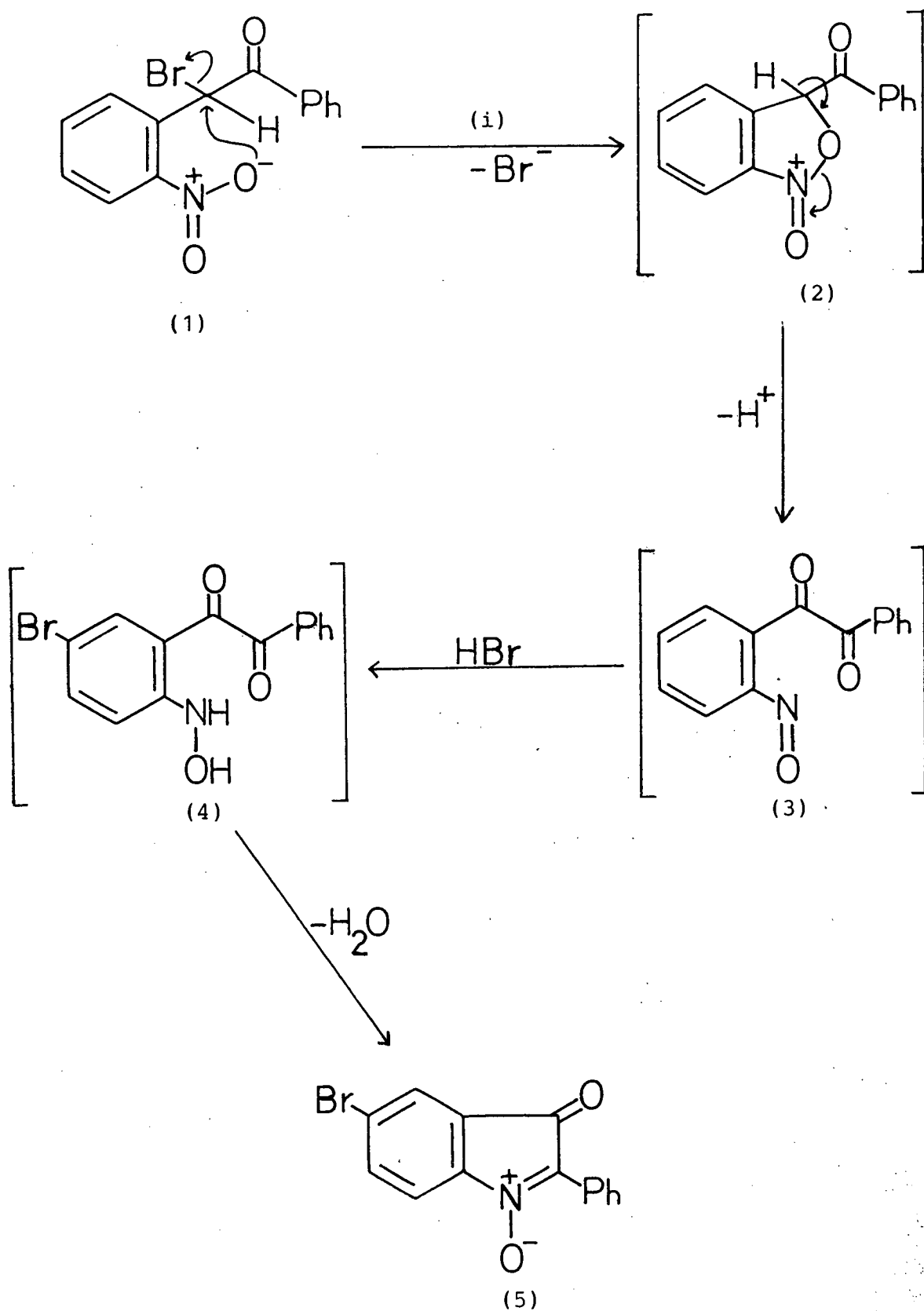
It has only been in recent years that the biological activity of isatogens has been investigated. Hooper et al⁴⁴ were the first workers to report (Scheme 25) that 2-phenylisatogen (94) and 2-(2-pyridyl)isatogen (125) showed significant broad spectrum antimicrobial activity against gram positive organisms. In comparison the corresponding indolones (126) and (127) lack bactericidal activity indicating that the N-oxide substituent is crucial for the antimicrobial properties of the isatogens (94) and (125). A variety of isatogen derivatives also exhibit fungicidal

activity.⁴⁵ Isatogen derivatives have also been shown⁴⁶ to function as smooth muscle relaxants and are reported⁴⁷ to exhibit antitubercular activity.

CHAPTER 2

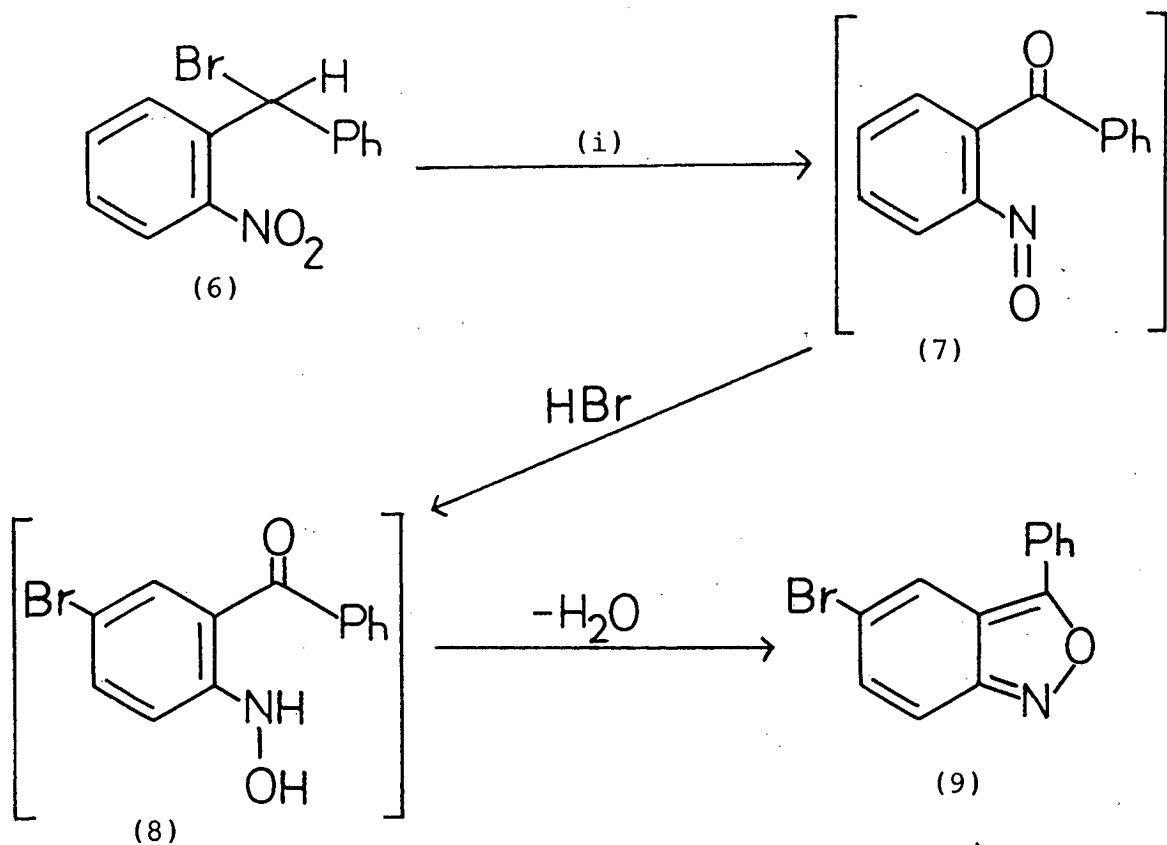
Studies of the Scope of a New General

Synthesis of $3H$ -Indol-3-one 1-N-Oxides (Isatogens)



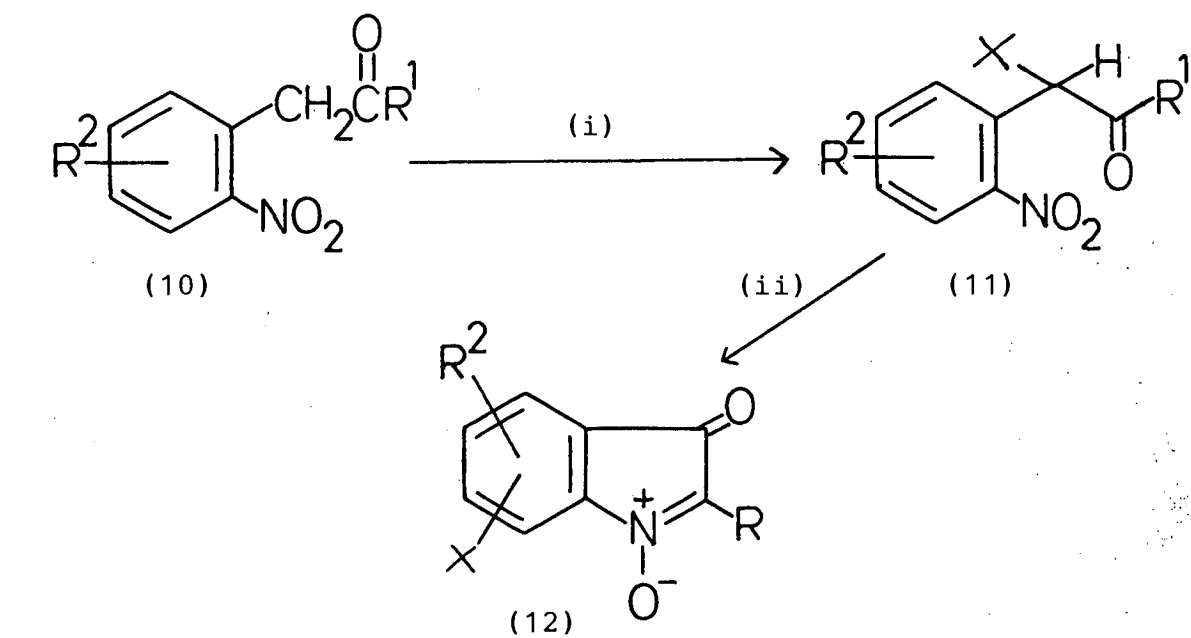
(i) AcOH , heat.

Scheme 1



(i) HBr, AcOH, heat.

Scheme 2



(i) X_2 .

(ii) H^+ .

(R^1 = alkyl, aryl, CO_2R)

(X = Cl, Br)

Scheme 3

Studies of the Scope of a New General Synthesis of 3H-Indol-3-one 1-N-oxides (Isatogens)

2.1 Introduction

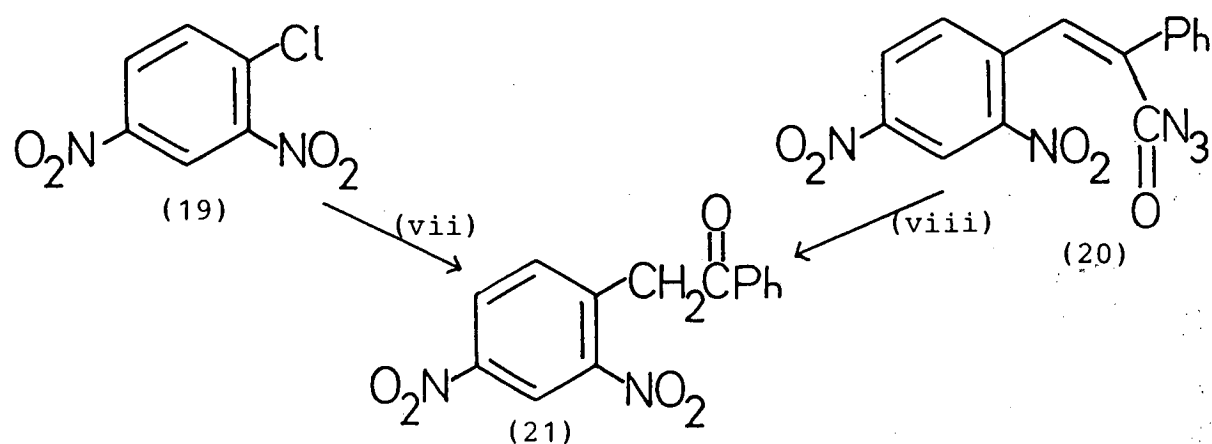
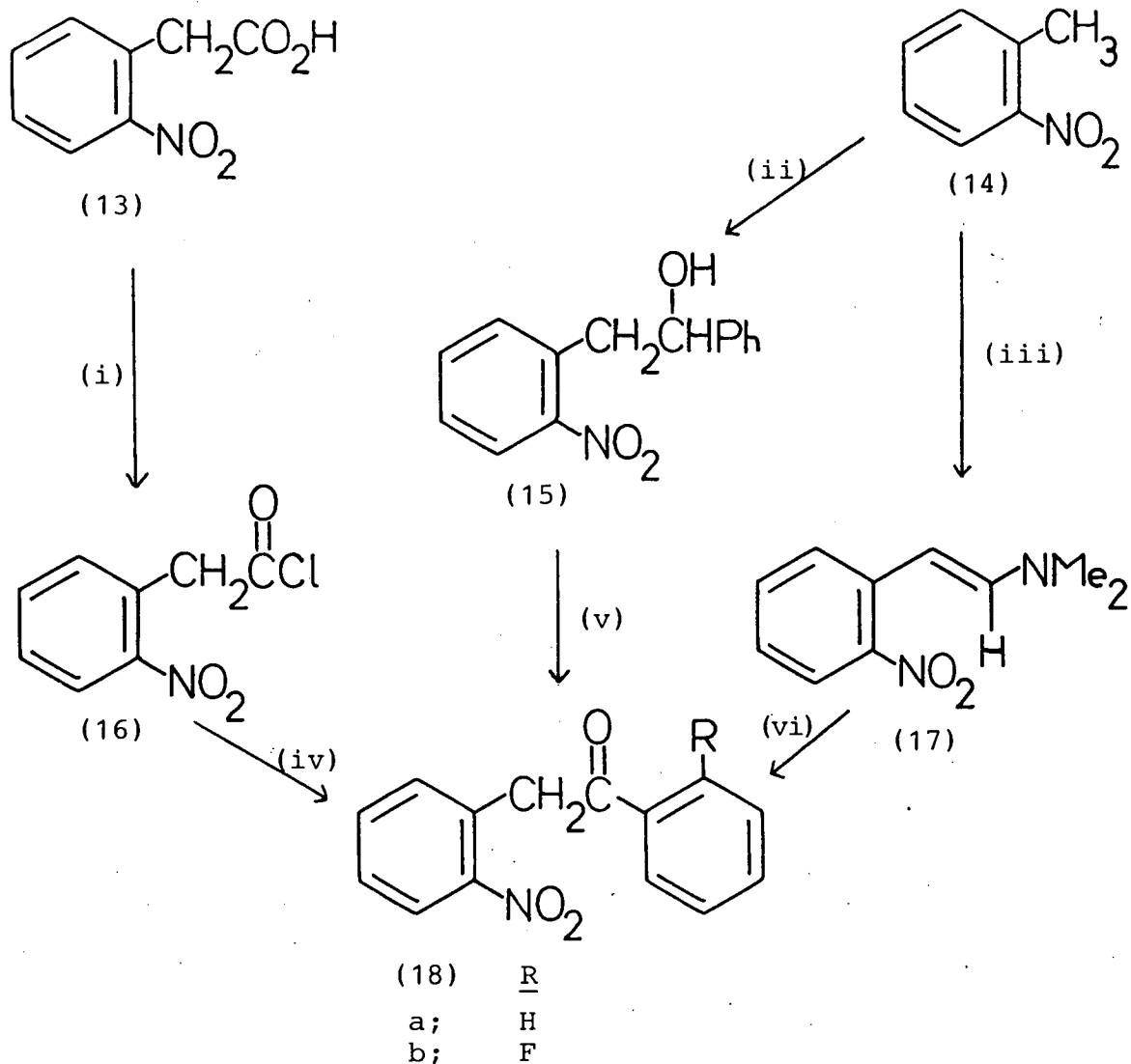
In the course of previous studies at Edinburgh, Steel⁴⁸ found (Scheme 1) that 2-bromo-2-(2-nitrophenyl)-1-phenyl-ethanone (1) when heated in glacial acetic acid unexpectedly underwent cyclisation in moderate yield (58%) to a product identified as 5-bromo-2-phenyl-3H-indol-3-one 1-N-oxide- (5-bromo-2-phenyl isatogen) (5). The formation of this product from the bromoketone can be explained by a mechanism (Scheme 1) involving the intramolecular nucleophilic displacement of the bromine substituent by an oxygen atom of the ortho-nitro-group to afford a cyclic intermediate (2) convertible by proton loss and ring-opening into 2-nitroso-benzil (3). The indirect reduction of the latter with introduction of bromine to give the hydroxyamino-derivative (4) followed by cyclisation then accounts for the formation of the isatogen (5). A similar mechanism (Scheme 2) has been proposed⁴⁹ to explain the acid-catalysed conversion of 2-nitrobenzhydryl bromide (6) via the intermediates (7) and (8) into 5-bromo-3-phenyl-2,1-benzisoxazole (9).

The detailed discussion in Chapter 1 showed isatogens to be an interesting class of indole derivatives whose detailed study has been limited to date because the available isatogen syntheses tend to lack generality and involve

relatively inaccessible starting-materials. The transformation [(1)→(5)] discovered by Steel⁴⁸ represents a particularly simple synthesis of an isatogen derivative and the object of the studies described in the present thesis was to develop a new general synthesis of isatogens (Scheme 3) based on a simple strategy of converting 2-(2-nitrophenyl)-ethanone derivatives into 2-halogeno-2-(2-nitrophenyl)-ethanones then acid-catalysed cyclisation of the latter [(10) → (11) → (12)]. The initial studies centred on the development of viable routes to 1-aryl-2-(2-nitro-aryl)ethanones (10; $R^1 = \text{aryl}$) and the derived 1-aryl-2-bromo-2-(2-nitroaryl)ethanones (11; $X = \text{Br}$, $R^1 = \text{aryl}$) and the acid-catalysed cyclisation of the latter to 2-aryl-isatogen derivatives (12; $R^1 = \text{aryl}$). Attempts were then made to develop related routes to 2-alkyl- and 2-acyl-isatogens (12; $R^1 = \text{alkyl or acyl}$) and also to heterocyclic analogues (12; heterocyclic nucleus for benzene nucleus).

2.2 Studies of Synthetic Routes to 1-Aryl-2-(2-nitro-aryl)ethanone Derivatives

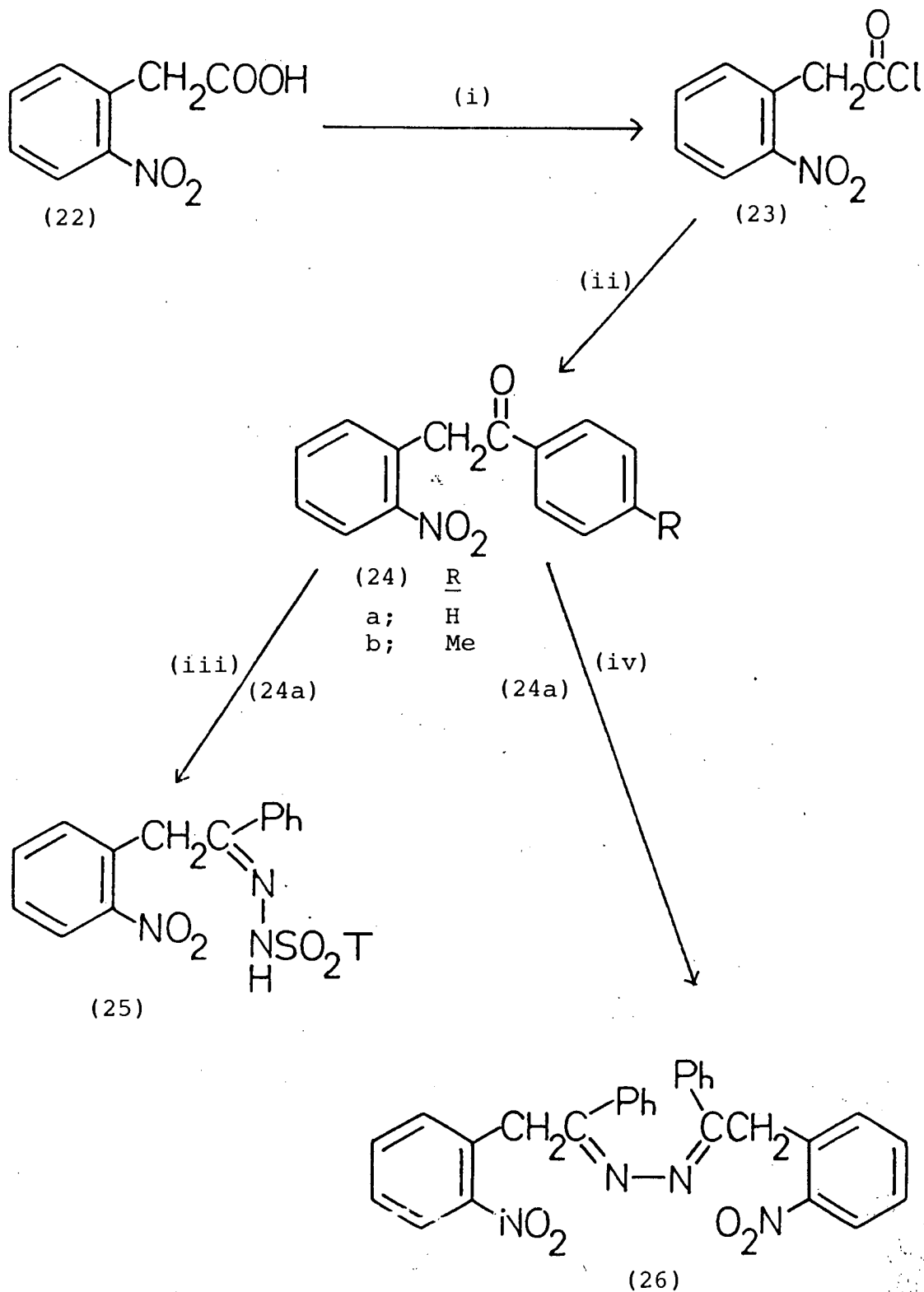
The development of a general route to 2-arylisatogens (12; $R^1 = \text{aryl}$) based on the synthetic approach outlined in Scheme 3 is dependant on the availability of 1-aryl-2-(2-nitroaryl)ethanones (10; $R^1 = \text{aryl}$) as the key starting-materials. Very few 1-aryl-2-(2-nitroaryl)ethanone derivatives have been reported in the literature. Two



- (i) SOCl_2 , reflux.
(ii) PhCHO , base.
(iii) $(\text{Me})_2\text{NCH}(\text{OEt})_2$, dimethylformamide, reflux.
(iv) benzene, AlCl_3 , reflux.
(v) conc. HNO_3 , CHCl_3 .
(vi) Et_3N , PhCOCl , reflux; H_2O , 1,4-dioxane, reflux.
(vii) $\text{PhC}(\text{O})\text{CH}(\text{Na}^+)\text{C}(\text{O})\text{Me}$, EtOH , reflux.
(viii) heat then H_2O .

syntheses (Scheme 4) have been reported for the parent compound, 2-(2-nitrophenyl)-1-phenylethanone (18a). Buza and Polaczkowa⁵⁰ obtained the ketone (18a) in 58% yield by the Friedel-Crafts reaction of benzene with 2-nitrophenylacetyl chloride (16). Bakke⁵¹ on the other hand synthesised 2-(2-nitrophenyl)-1-phenylethanone (18a) in high yield (98%) by the oxidation of 2-(2-nitrophenyl)-1-phenylethanol (15) readily available by the base-catalysed condensation of 2-nitrotoluene (14) with benzaldehyde. Another approach by Garcia and Fryer⁵² in which they prepared the ortho-fluoro-derivative (18b) by the triethylamine catalysed reaction of the easily accessible⁵³ enamine (17) with benzoyl chloride. 2-(2,4-Dinitrophenyl)-1-phenylethanone (21) has been obtained in moderate yield (50-65%) by the reaction⁵⁴ of 2,4-dinitrochlorobenzene (19) with the sodium salt of benzoylacetone and the thermolysis⁵⁵ of the azidoacylalkene (20).

In the present studies it was decided initially to obtain the required 1-aryl-2-(2-nitroaryl)ethanones (10; $R^1 = \text{aryl}$) by extensions of the Buza and Polaczkowa synthesis⁵⁰ involving the Friedel-Crafts reactions of substituted 2-nitrophenylacetyl chlorides with benzene derivatives.



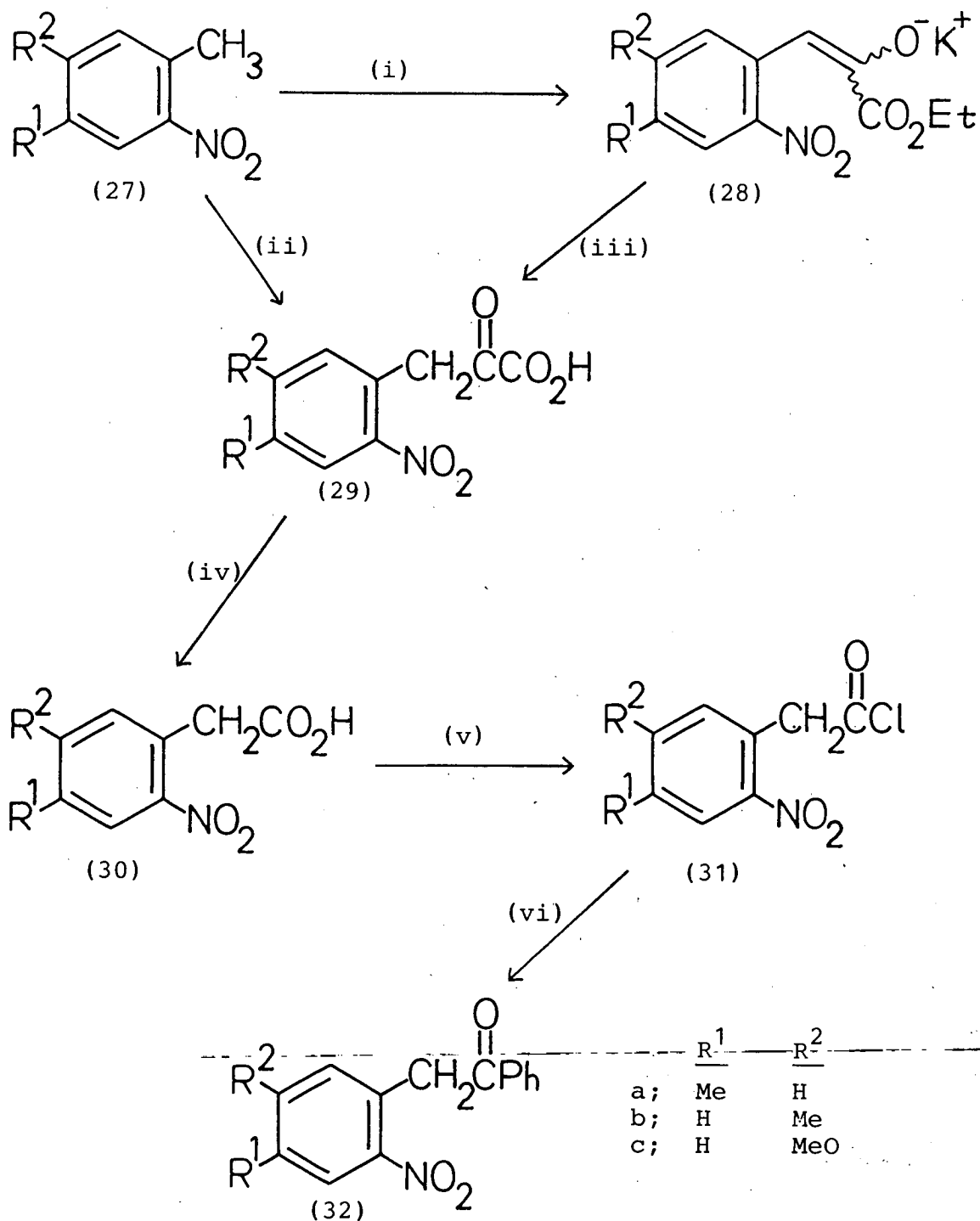
- (i) SOCl_2 , reflux.
 (ii) benzene or toluene, AlCl_3 , reflux.
 (iii) $4\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHNH}_2$, MeOH, reflux.
 (iv) $\text{H}_2\text{N.NH}_2\cdot\text{HCl}$, EtOH, reflux.

Scheme 5

2.2.1 Synthesis of 1-aryl-2-(2-nitroaryl)ethanones
based on Friedel-Crafts reactions of 2-nitro-
phenylacetyl chlorides

The synthesis (Scheme 5) of the known parent ketone, 2-(2-nitrophenyl)-1-phenyl ethanone (24a) was readily accomplished in good yield (64%) by the known⁵⁶ conversion of 2-nitrophenylacetic acid (22) into 2-nitrophenylacetyl chloride (23) followed by Friedel-Crafts reaction of the latter compound with benzene in the presence of aluminium trichloride as described by Steel⁴⁸ following on the work of Buza and Polaczkowa.⁵⁰ The ketone (24a) was characterised by its melting-point which was consistent with the literature⁴⁸ value and by the melting point of its oxime derivative which was identical with the value reported by Steel.⁴⁸ The ketone (24a) was further characterised by its reaction with toluene-4-sulphonylhydrazine (tosylhydrazine) to give a good yield of the tosylhydrazone (25) which analysed correctly and showed spectroscopic properties consistent with its structure. In contrast, heating 2-(2-nitrophenyl)-1-phenylethanone (24a) with hydrazine hydrate in ethanol afforded, in addition to unreacted starting-material, a low yield of product which is formulated as the azine (26) on the evidence of its combustion analysis and its mass and ¹H n.m.r. spectra.

In contrast to the reaction with benzene, the Friedel-Crafts reaction of toluene with 2-nitrophenylacetyl chloride (23) afforded, in addition to intractable gums and oils only a low yield (25%) of the expected ketone (24b) whose



- (i) $(\text{COOEt})_2$, KOEt, ether, reflux.
 (ii) $(\text{COOEt})_2$, NaOMe or NaOEt or KOEt, ether, reflux then NaOH at room temp.
 (iii) H_2O , dil. HCl, room temp.
 (iv) NaOH, H_2O_2 , 10° .
 (v) SOCl_2 , benzene, 45° .
 (vi) benzene, AlCl_3 , reflux.

Scheme 6

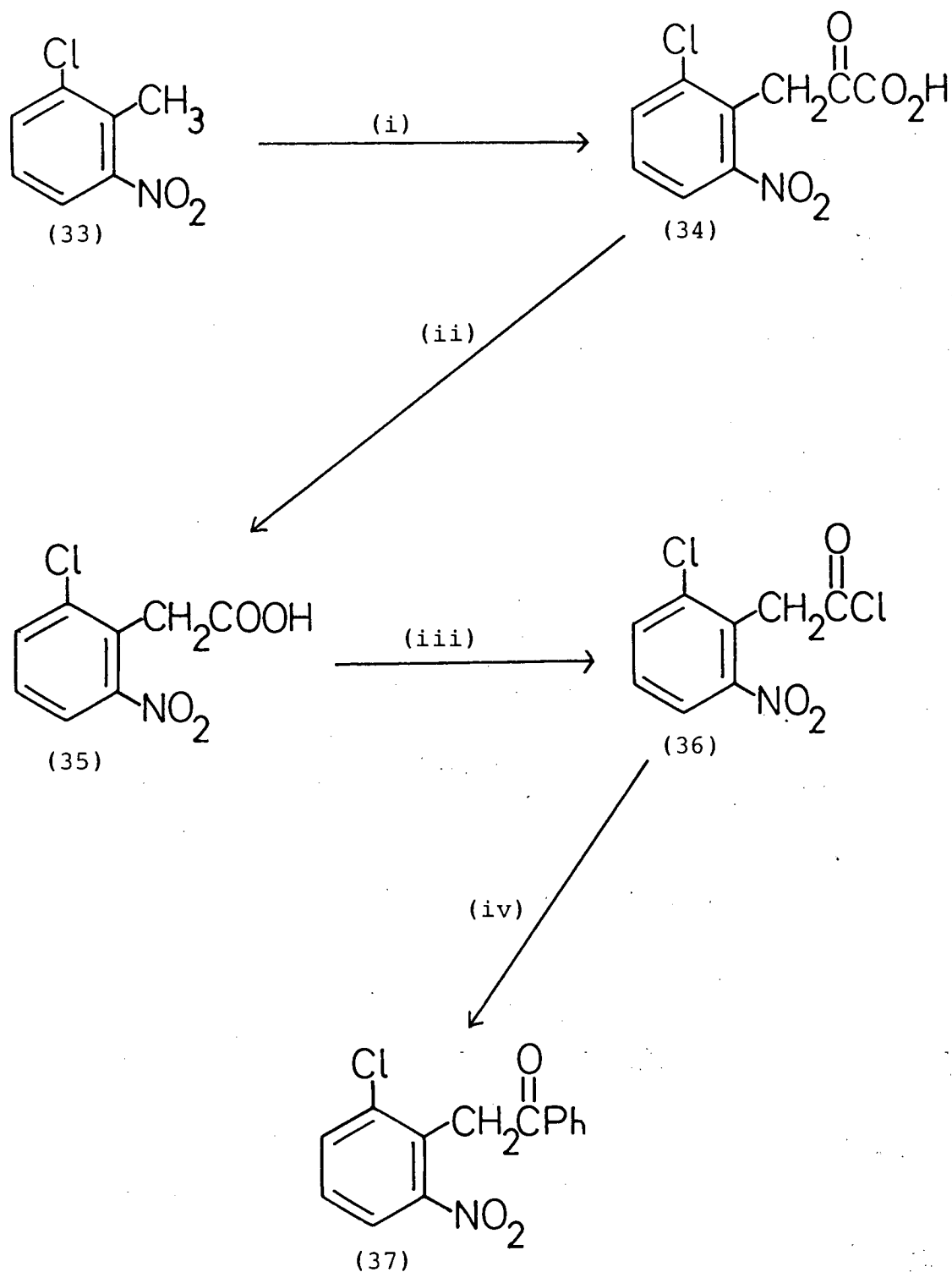


analytical and spectroscopic properties were consistent with its structure. The low yield of this reaction is surprising since, in comparison to benzene, toluene, with its electron-donating methyl substituent would have been expected to be more reactive towards the Friedel-Crafts acylation and consequently to give a better yield of the ketone product compared with benzene.

The extension of the Buza-Polaczkowa method⁵⁰ (Scheme 5) to the general synthesis of 1-aryl-2-(2-nitroaryl)ethanones is dependent on the availability of substituted 2-nitrophenylacetic acids. The synthetic methods for these compounds were therefore next investigated (Scheme 6). Substituted 2-nitrophenylacetic acids (30) are generally available⁵⁷⁻⁶¹ by the hydrogen-peroxide oxidation of 3-(2-nitroaryl)-2-oxopropanoic acids (29) which are accessible in turn⁵⁷⁻⁶¹ by the sodium or potassium methoxide or ethoxide catalysed condensation of 2-nitrotoluene derivatives (27) with diethyl oxalate followed by hydrolytic work-up. Simchen and Hafner⁶² have shown that the alkoxide-catalysed condensation of the 2-nitrotoluene derivatives (27) with diethyl oxalate and the subsequent hydrogen peroxide oxidation of the resulting 3-(2-nitroaryl)-2-oxopropanoic acids (29) can be combined to provide a 'one pot' synthesis, though low yield of substituted 2-nitrophenylacetic acids (30). Contrary to the result obtained by Simchen and Hafner⁶² it was found in practice that the sodium methoxide catalysed condensation of 1,3-dimethyl-4-nitrobenzene (27b) with diethyl oxalate

followed by in situ hydrolysis to the corresponding 3-(2-nitroaryl)-2-oxopropanoic acid (29b) and in situ hydrogen peroxide oxidation of the latter gave only complex mixtures and none of the expected⁶² 5-methyl-2-nitrophenylacetic acid (30b). However, a similar series of transformations starting with 3-methyl-4-nitroanisole (27c) gave a low yield (13%) of 5-methoxy-2-nitrophenylacetic acid (30c) whose melting-point closely agreed with that reported in the literature⁵⁸ for the 2-nitrophenylacetic acid derivative (30c). Because of the unpredictable nature and low yield of the 'one pot' synthesis of 2-nitrophenylacetic acids (30) from the 2-nitrotoluene derivatives (27) it was decided to use the standard procedure⁵⁷⁻⁶¹ of synthesising the 3-(2-nitroaryl)-2-oxopropanoic acids (29) and after their isolation to ^{convert}oxidatively into the required 2-nitrophenylacetic acids (30).

The known⁵⁷⁻⁵⁹ 3-(2-nitroaryl)-2-oxopropanoic acids (29a-c) were all obtained by a method first described by Reissert and Scherk⁵⁷ where the sodium ethoxide catalysed condensation of the corresponding 2-nitrotoluene derivatives (27a-c) ^{was} followed by hydrolytic work up with sodium hydroxide. This procedure afforded 3-(4-methyl-2-nitrophenyl)-2-oxopropanoic acid (29a) in moderate yield (39%) and 3-(5-methoxy-2-nitrophenyl)-2-oxopropanoic acid (29c) in good yield (63%) with melting points consistent with the literature values.^{58,59} The application of the Reissert-Scherk method to the synthesis of 3-(5-methyl-2-nitrophenyl)-



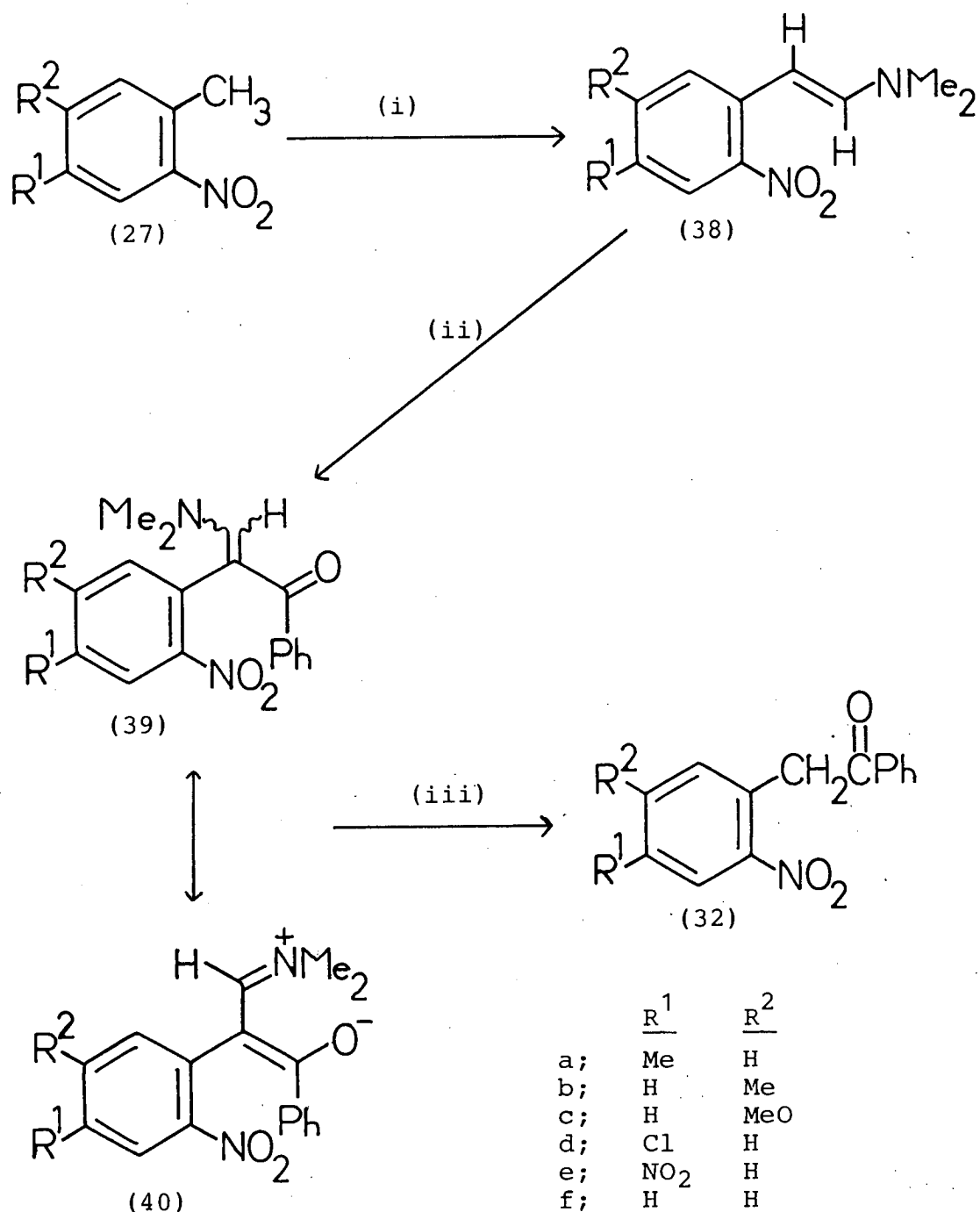
- (i) $(\text{COOEt})_2$, KOEt, ether, reflux, then H_2O , room temp.
(ii) NaOH, H_2O_2 , 10° .
(iii) SOCl_2 , benzene, 45° .
(iv) benzene, AlCl_3 , reflux.

Scheme 7

2-oxopropanoic acid (29b) gave a good yield (70%) of a product whose mass and i.r. spectra were consistent with the structure (29b) but whose melting-point despite repeated attempts to crystallise it was ca. 50° below the literature⁵⁷ value. The accuracy of the melting-point for 3-(5-methyl-2-nitrophenyl)-2-oxopropanoic acid (29b) obtained in the present studies was verified by its synthesis using an alternative procedure. This involved the use⁵⁸ of potassium ethoxide to effect the condensation of 1,3-dimethyl-4-nitrobenzene (27b) with diethyl oxalate to afford a good yield of the potassium enolate (28b). After isolation this was hydrolytically converted into the keto-acid (29b) in excellent yield (93%) using the procedure described by DiCarlo⁶³. 3-(5-Methyl-2-nitrophenyl)-2-oxopropanoic acid (29b) obtained by this method had the same melting-point as the product of the sodium ethoxide-catalysed condensation of 1,3-dimethyl-4-nitrobenzene (27b) with diethyl oxalate, indicating that the literature⁵⁷ melting point for the keto-acid (29b) is incorrect. The improved yield of the keto-acid (29b) obtained using potassium ethoxide rather than sodium ethoxide as the condensation catalyst confirms the claim by Blaikie and Perkin⁵⁸ that potassium ethoxide is in general the better catalyst for the condensation of 2-nitrotoluene derivatives with diethyl oxalate. However, it was found (Scheme 7) that the condensation of the commercially available 2-chloro-6-nitrotoluene (33) with diethyl oxalate in the presence of potassium ethoxide followed by hydrolytic work-up gave a low yield (42%)

of the known⁶⁰ 3-(2-chloro-6-nitrophenyl)-2-oxopropanoic acid (34). The low yield afforded in this case may be due to the sterically hindered nature of the methyl substituent.

Having obtained the keto-acids (29a-c) and (34) it was necessary to oxidatively decarboxylate them to the required substituted 2-nitrophenylacetic acids (30a-c) and (35). This was readily accomplished using hydrogen peroxide in aqueous sodium hydroxide under standard conditions,⁶¹ and afforded good to excellent yields of the known^{57,58,60,61,62} 2-nitrophenylacetic acid derivatives (30a-c) and (35) which with the exception of the 5-methyl-compound (30b) gave melting-points consistent with the literature values.^{58,60,61} The melting point of 5-methyl-2-nitrophenylacetic acid (30b) found in the present studies (127°) was very much lower than the literature value (149°).^{58,62} However, the i.r. and mass spectra of the product obtained in the present work verified its identity as 5-methyl-2-nitrophenylacetic acid (30b). In a similar method⁴⁸ as for 2-nitrophenylacetic acid, 4-methyl-2-nitrophenylacetic acid (30a) was treated with thionyl chloride in benzene to afford a solution of the acid chloride (31a) which reacted in turn with aluminium trichloride to give the expected ketone (32a) though only in low yield (45%). The previously unknown ketone (32a) gave analytical data and spectroscopic properties fully consistent with the assigned structure. Surprisingly,



- (i) $(Me)_2NCH(OMe)_2$ or $(Me)_2NCH(OEt)_2$, dimethylformamide, reflux.
(ii) $PhCOCl$, Et_3N , toluene, reflux.
(iii) H_2O , 1,4-dioxane, reflux.

Scheme 8

the attempted synthesis of the ketone (32c) from 5-methoxy-2-nitrophenylacetic acid (30c) by initial reaction with thionyl chloride and subsequently with aluminium trichloride in benzene gave only a low yield of a multicomponent oil which yielded no identifiable material. A similar treatment (Scheme 7) of 2-chloro-6-nitrophenylacetic acid (35) afforded only a low yield (22%) of the expected ketone (37) whose analytical and spectroscopic properties were in accord with its structure. A substantial quantity of unreacted 2-chloro-6-nitrophenylacetic acid (35) was obtained indicating a low Friedel-Crafts reactivity of the corresponding acid chloride (36) possibly due to steric hindrance by the ortho substituents.

2.2.2 Synthesis of 1-aryl-2-(2-nitroaryl)ethanones based on acylation reactions of 1-(N,N-dimethylamino)-2-(2-nitroaryl)ethenes

Because of the apparent inefficiency of the Friedel-Crafts reactions of substituted 2-nitrophenylacetyl chlorides with benzene found in the present studies, it was decided to find an alternative method for the efficient general synthesis of the required 1-aryl-2-(2-nitroaryl)ethanones (32). The method chosen (Scheme 8) was based on the known⁵³ reaction of 2-nitrotoluene (27f) with dimethylformamide dimethyl acetal to afford 1-(N,N-dimethylamino)-2-(2-nitrophenyl)-ethene (38f). This enamine has been shown⁵² to undergo a triethylamine catalysed acylation with 2-fluorobenzoyl chloride to afford after in situ hydrolysis of the acylated

enamine (39; $R^1 = R^2 = H$, 2-FC₆H₄ for Ph), a moderate yield (45%) of 1-(2-fluorophenyl)-2-(2-nitrophenyl)-ethanone (32; $R^1 = R^2 = H$, 2-F.C₆H₄ for Ph). In the present investigations the triethylamine catalysed reaction of enamines (38), obtained from 2-nitrotoluene derivatives (27), with aroyl chlorides, followed by hydrolysis of the resulting acylated enamines (39) has been found to be a useful and essentially 'one-pot' method for the general synthesis of 1-aryl-2-(2-nitroaryl)ethanones (32) from readily accessible 2-nitrotoluene starting-materials.

Heating 2-nitrotoluene (27f) with dimethylformamide dimethyl acetal in dimethylformamide gave 1-(N,N-dimethyl-amino)-2-(2-nitrophenyl)ethene (38f) as a viscous red oil which was reacted without purification, with benzoyl chloride in toluene in the presence of triethylamine. Direct hydrolysis of the resulting oily product in aqueous 1,4-dioxane afforded the 2-(2-nitrophenyl)-1-phenylethanone (24a) identical in all respects to a sample prepared by the Friedal-Crafts methods (see before). Though the yield of the ketone (32f) obtained by the enamine procedure was only 25%, the essentially 'one pot' nature of the method prompted its application to the synthesis of other 1-aryl-2-(2-nitroaryl)ethanones (32).

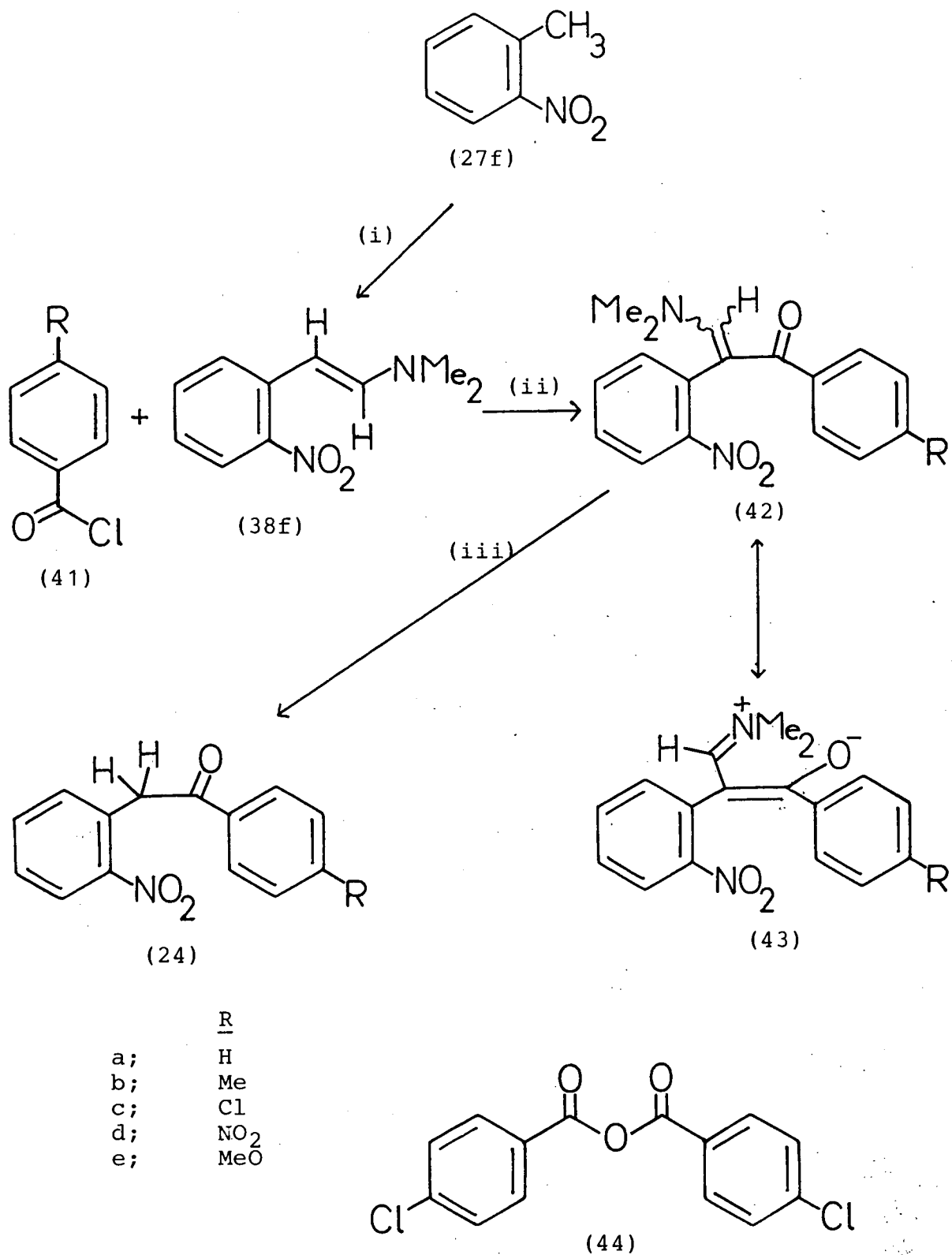
The reaction of 1,4-dimethyl-2-nitrobenzene (27a) and 1,3-dimethyl 4-nitrobenzene (27b) with dimethylformamide dimethyl acetal afforded the oily enamines (38a) and (38b).

These were reacted without purification as before with benzoyl chloride in the presence of triethylamine and the oily products obtained, hydrolysed to afford moderate yields (35-46%) of the expected ketones (32a) and (32b). The former compound was identical in all respects to the sample obtained by the Friedal-Crafts method (see before). The previously unknown ketone (32b) gave analytical and spectroscopic data fully in accord with its assigned structure.

The significantly increased yields of the ketones (32a) and (32b) compared to the parent ketone (32f) suggest that electron-donating substituents in the 2-nitrotoluene derivative (27) facilitate its conversion into the corresponding 1-aryl-2-(2-nitroaryl)ethanone (32). This substituent effect is readily explained since electron-donating 2-aryl substituents by increasing the electron-density at the 2-position will facilitate acylation of the enamine (38) at this site. This effect of the electron-donating substituents in the 2-aryl nucleus was further demonstrated by the behaviour of the enamine (38c), derived from 3-methyl-4-nitroanisole (27c), towards acylation. In this case two acylation products were obtained in greater than 80% overall yield. The higher melting product was isolated in moderate yield (47%) before the hydrolysis stage of the 'one pot' procedure which gave a combustion analysis and a mass spectrum that showed a parent ion at m/z 326 consistent with its formulation as the acylated enamine precursor (39c) of the ketone (32c). The latter was

also isolated (yield 39%) after the final hydrolysis stage and was identified on the result of its combustion analysis, its mass, i.r. and ^1H n.m.r. spectra and its conversion into the oxime derivative (32c; $\text{C} = \text{NOH}$ for $\text{C}=\text{O}$). The acylated enamine (39c) in agreement with its assigned structure, showed a six-proton singlet at δ 2.75 in its ^1H n.m.r. spectrum which was attributed to the dimethylamino-substituent. However, the low i.r. carbonyl frequency (1630 cm^{-1}) of the benzoyl substituent in the acylated enamine (39c) indicates a significant contribution to its structure by the betaine form (40). The overall structure of the acylated enamine (39c) was firmly established by its hydrolysis to the ketone (32c) in high yield (80%) after its heating under reflux in aqueous 1,4-dioxane.

In accord with the electron-withdrawing effect of its chloro-substituent, 4-chloro-2-nitrotoluene (27d) reacted with dimethylformamide dimethyl acetal followed by benzoyl chloride in the presence of triethylamine and subsequent hydrolysis to give only a low yield (21%) of the expected ketone (32d). This compound gave analytical data and showed spectroscopic properties fully in accord with the assigned structure. The attempted application of the enamine procedure to 2-chloro-6-nitrotoluene (33) gave only starting-material (41%) and a series of complex oils and gums with no evidence for the formation of the required ketone (37) which was previously obtained in low yield



- (i) $(\text{Me})_2\text{NCH}(\text{OMe})_2$ or $(\text{Me})_2\text{NCH}(\text{OEt})_2$, dimethylformamide, reflux.
 (ii) Et_3N , toluene, reflux.
 (iii) H_2O , 1,4-dioxane, reflux.

Scheme 9

(22%) by the Friedal-Crafts method. The total failure of the enamine procedure in this particular case can be attributed to the inhibition of acylation by the combined effects of electron-withdrawal by the chloro-substituent and the steric effect of the ortho-chloro- and nitro-substituents.

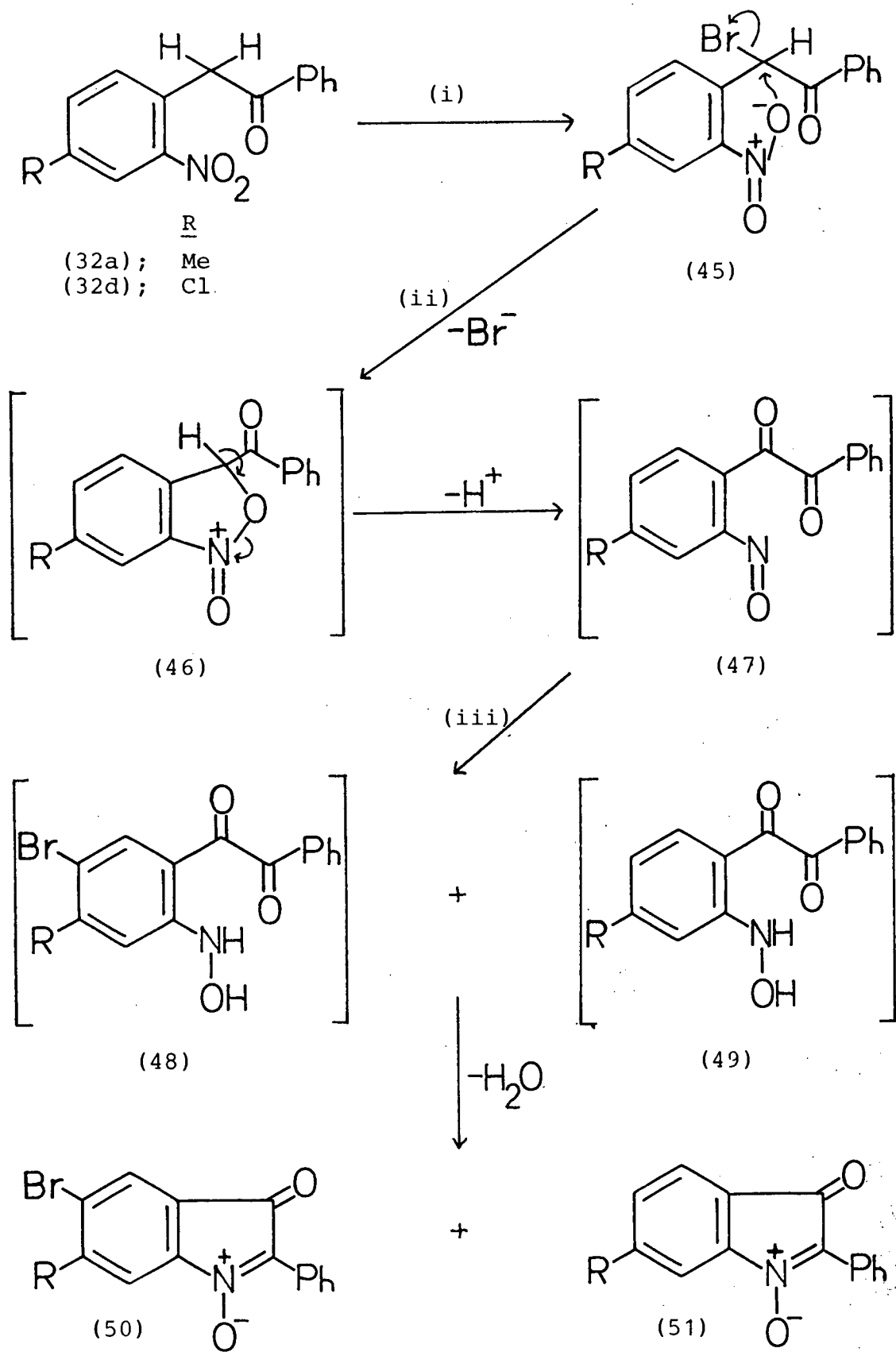
The electron-withdrawing substituents of the aroyl chloride also had an apparently inhibiting effect on its ability to acylate the enamine. Thus (Scheme 9) the enamine (38f), obtained by the reaction of 2-nitrotoluene (27f) with dimethylformamide dimethyl acetal, underwent the triethylamine-catalysed reaction with 4-chlorobenzoyl chloride (41c) and 4-nitrobenzoyl chloride (41d) followed by hydrolysis to give in the former case none of the expected ketone (24c) and in the latter only a 7% yield of the nitro-derivative (24d). The only products isolated in this reaction of the enamine (38f) with 4-chlorobenzoyl chloride (41c) were 4-chlorobenzoic anhydride (44) (30%) and unreacted 2-nitrotoluene (27f) (28%).

The foregoing studies demonstrate that the reaction of 2-nitrotoluene derivatives (27) with dimethylformamide dimethyl acetal followed by the triethylamine catalysed aroylation of the resulting enamines (38) and subsequent hydrolysis of the acylated products (39) is a viable method for the general synthesis of 1-aryl-2-(2-nitroaryl)-ethanones (32). However, the yields were disappointing and since this could be partly due to the thermal instability

of dimethylformamide dimethyl acetal it was decided to investigate the effect of using the more thermally stable dimethylformamide diethyl acetal as the reagent in the enamine forming step [(27) \rightarrow (38)]. In practice (Scheme 8) the use of dimethylformamide diethyl acetal in place of the dimethyl acetal in the synthesis of the parent ketone (32f) resulted in a significant increase in the yield of the latter from 25 to 38%. In the conversion of 4-chloro-2-nitrotoluene (27d) into 2-(4-chloro-2-nitrophenyl)-1-phenylethanone (32d), the yield was increased dramatically from 21 to 50%. However, this apparent improvement in efficiency for the conversion of a 2-nitrotoluene derivative with an electron-withdrawing chloro-substituent (see before) into the corresponding 1-aryl-2-(2-nitroaryl)ethanone did not extend to 2,4-dinitrotoluene (27e). The reaction of this compound with dimethylformamide diethyl acetal followed by benzoyl chloride in the presence of triethylamine and hydrolysis of the resulting oily product afforded only a very poor yield (1%) of the known^{54,55} ketone (32e) - the identity of which was firmly established by its analytical and spectroscopic properties.

The use of dimethylformamide diethyl acetal instead of the dimethyl acetal significantly improved the efficiency of the conversion (Scheme 9) of 2-nitrotoluene (27f) into the 1-(4-substituted aryl)-2-(2-nitroaryl)-ethanones (24). An interesting development of these

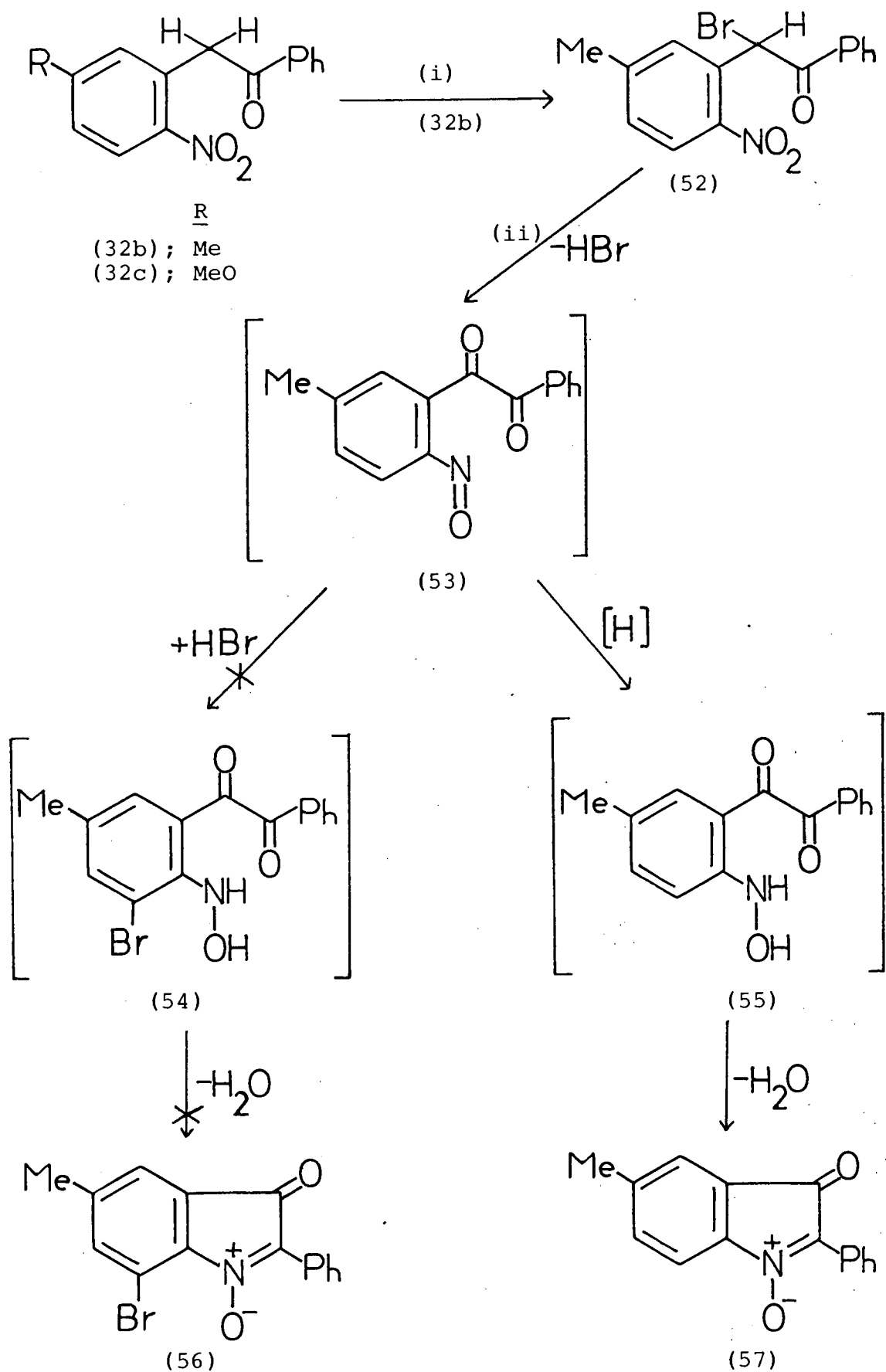
dimethylformamide diethyl acetal promoted reactions was the ready isolation, before the hydrolysis step, of the acylated amines (42) as the major reaction products. Thus, in contrast to the failure of the attempted synthesis of 1-(4-chlorophenyl)-2-(2-nitrophenyl)ethanone (24c) from 2-nitrotoluene (27f) using dimethylformamide dimethyl acetal, the use of the diethyl acetal under identical reaction conditions afforded both the acylated enamine (42c) (31%) and the expected ketone (24c) (20%). The acylated enamine (42c) gave analytical and mass spectral data consistent with its structure which was also supported by its i.r. and ^1H n.m.r. absorption. The structure of the acylated enamine (42c) was further verified by its hydrolysis in aqueous 1,4-dioxane to give the ketone (24c) in high yield (72%). The analytical and spectroscopic properties of the ketone (24c) were fully consistent with its structure. The use of dimethylformamide diethyl acetal instead of the dimethyl acetal also caused a dramatic increase in the efficiency of the conversion of 2-nitrotoluene (27f) into 1-(4-nitrophenyl)-2-(2-nitrophenyl)ethanone (24d). The only product isolated in good yield (57%) from this reaction was the acylated enamine (42d) which was identified on the results of its analytical and spectroscopic properties and its subsequent hydrolysis in aqueous 1,4-dioxane to give the ketone (24d) in high yield (86%). The analogous reaction of 2-nitrotoluene (27f) with dimethylformamide diethyl acetal followed by 4-methoxybenzoyl chloride (41e) afforded



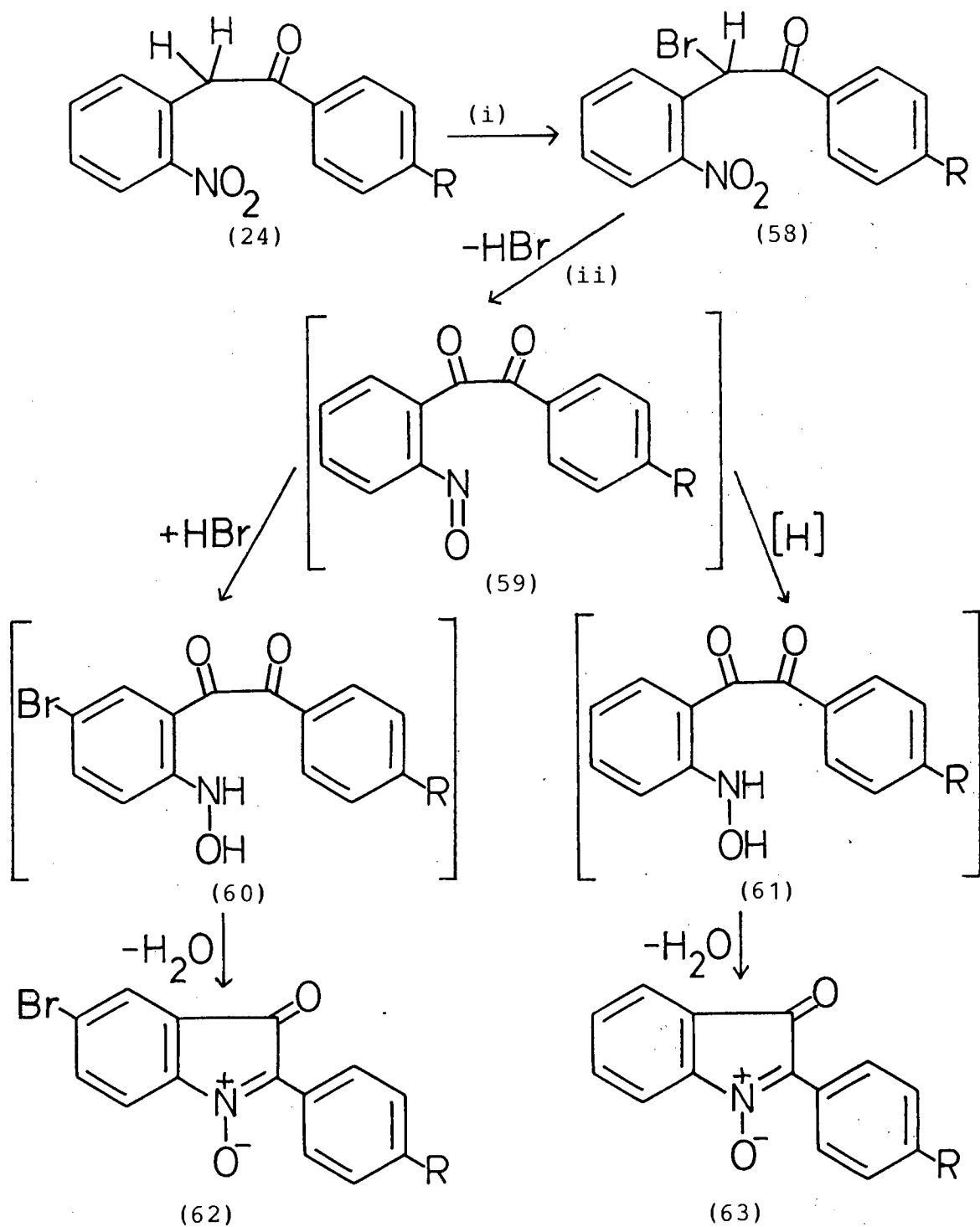
(i) Br_2 , 1,2-dimethoxyethane, room temp.
(ii) AcOH , heat, or AcOH , hydroquinone, heat.
(iii) HBr .

R
a; Me
b; Cl

Scheme 10



(i) Br₂, 1,2-dimethoxyethane, room temp.
 (ii) AcOH, heat or AcOH, hydroquinone, heat.



	<u>R</u>
a;	H
b;	Me
c;	Cl
d;	NO ₂
e;	MeO

(i) Br₂, 1,2-dimethoxyethane, room temp.
 (ii) AcOH, heat or AcOH, hydroquinone, heat.

Scheme 12

a single product in moderate yield (49%) whose analytical and spectroscopic data were fully in accord with the acylated enamine structure (42e). As expected, the heating of this compound in aqueous 1,4-dioxane resulted in its hydrolysis to the ketone (24e) in excellent yield (93%). In contrast to the result obtained with 4-methoxybenzoyl chloride (41e), 2-nitrotoluene (27f) reacted with dimethylformamide diethyl acetal followed by 4-methylbenzoyl chloride (41b) to give after hydrolysis only complex oils and gums as well as a low recovery (17%) of the starting-material (27f). There was no evidence for the formation of this reaction of the ketone (24b) previously obtained by the Friedal-Crafts method (see before).

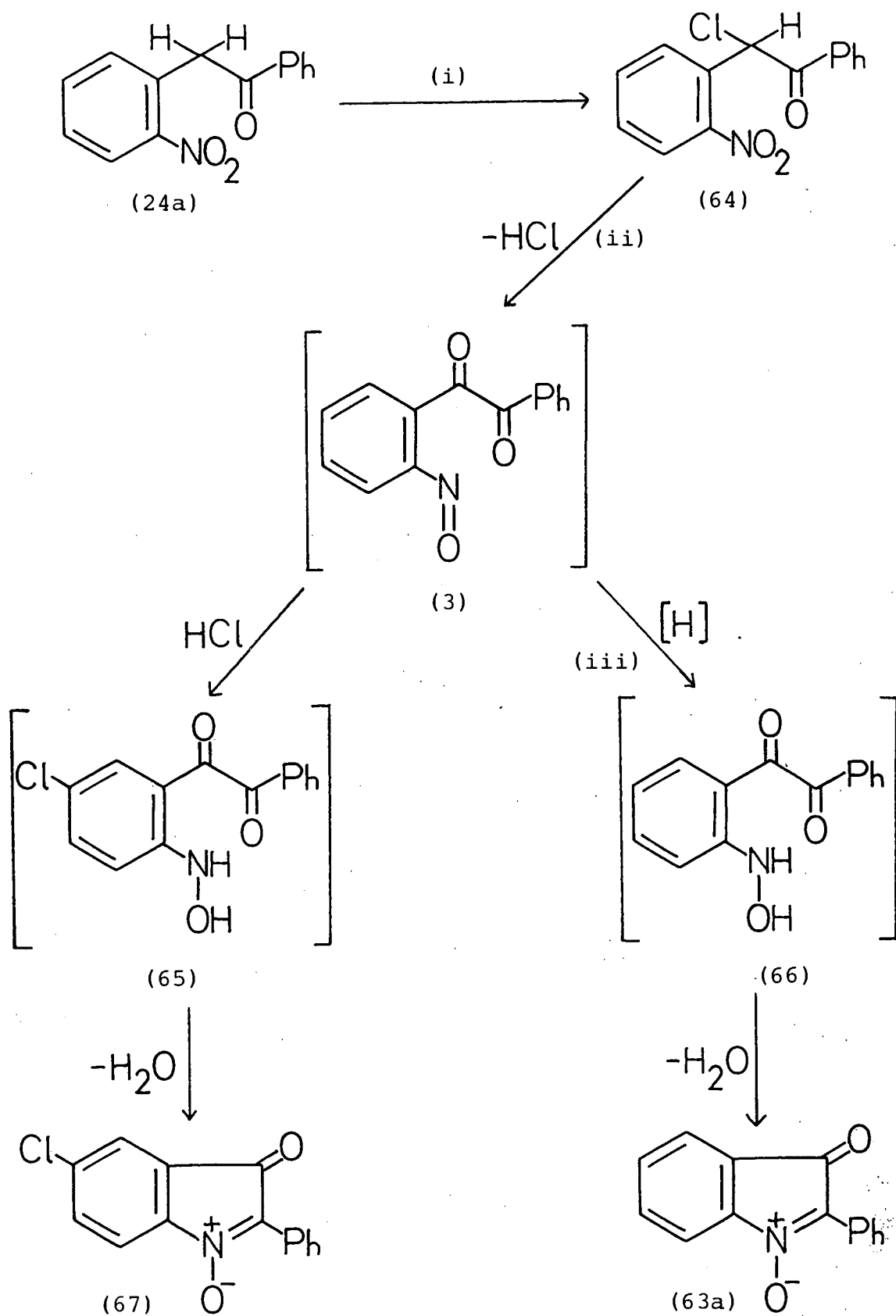
2.3 Studies of the Halogenation Reactions of 1-Aryl-2-(2-nitroaryl)ethanones

The 1-aroyl-2-(2-nitroaryl)ethanones (24a-e) and (32a-d) having been successfully obtained, the next step (Schemes 10, 11 and 12) was to synthesise their corresponding 1-aryl-2-bromo-2-(2-nitrophenyl)ethanones. The parent 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (58a) has already been reported in the literature⁶⁴ as the product of the reaction of 2-(2-nitrophenyl)-1-phenylethanone (24a) with molecular bromine. In the present work (Scheme 12) it was found that the ketone (24a) reacted smoothly with bromine in 1,2-dimethoxyethane at room temperature to afford an excellent (91%) yield of the α -bromoketone (58a) with a melting-point identical to the literature value.⁶⁴ The 1-aryl-2-

(2-nitroaryl)ethanone derivatives (32a), (32b) and (32d) reacted similarly with bromine in 1,2-dimethoxyethane at room temperature (Schemes 10 and 11) to afford uniformly high yields (92-96%) of the corresponding α -bromo-ketones (45a), (52) and (45b). The structures of these compounds were positively established by their analytical data and their i.r. and ^1H n.m.r. spectra. The latter, in particular, lacked absorption due to the protons of a methylene substituent but contained a proton singlet at $\delta 7.07-7.16$ which was assigned to the methine proton which is strongly deshielded by the combined electron-withdrawing effects of the bromo- and keto-substituents. 2-Bromo-2-(4-methyl-2-nitrophenyl)-1-phenylethanone (45a) showed unusual mass spectral behaviour. The F.A.B. mass spectrum contained peaks at m/z 336 and 334 due to $(M+H)^+$ species derived from the two isotopic parent ions. In contrast the peak of highest mass in the electron impact mass spectrum occurred at m/z 237 corresponding to the loss of hydrobromous acid from the two isotopic parent ions. The peaks of highest mass at m/z 289 and 287 in the electron impact mass spectrum of 2-bromo-2-(5-methyl-2-nitrophenyl)-1-phenylethanone (52) can be attributed to fragment ions obtained by loss of the nitro-group from the two isotopic parent ions.

In marked contrast to the ketones (32a), (32b) and (32d), 2-(5-methoxy-2-nitrophenyl)-1-phenylethanone (32c) and 2-(6-chloro-2-nitrophenyl)-1-phenylethanone [Scheme 7; (37)] failed to give the corresponding α -bromo-ketones on attempted reaction with bromine in 1,2-dimethoxyethane at room temperature. In the case of the methoxy compound (32c) the product obtained from the bromination was an unstable red solid which decomposed on attempted purification. The chloro-compound (37) on the other hand largely failed to react and was recovered unchanged (yield 56%) together with an intractable oil. The apparent reluctance of 2-(6-chloro-2-nitrophenyl)-1-phenylethanone (37) to brominate may be due to steric hindrance by the ortho-chloro- and nitro-substituents.

The bromination of the 1-(4-substituted aryl)-2-(2-nitrophenyl)ethanones (24b), (24c) and (24d) using bromine in 1,2-dimethoxyethane at room temperature proceeded as expected to give high yields (84-92%) of the respective α -bromo-ketones (58b), (58c) and (58d). The structures of these compounds were confirmed by their combustion analyses and their i.r. and ^1H n.m.r. spectra, the latter containing a one-proton singlet at δ 7.07-7.12 due to the strongly deshielded hydrogen of the methine substituent. The electron impact mass spectrum of 2-bromo-1-(4-chlorophenyl)-2-(2-nitrophenyl)ethanone (58c) lacked a peak due to the parent ion, the ions of highest mass at m/z 259



(i) SO₂Cl₂, pyridine, toluene, heat.
(ii) AcOH, heat or HCl.g, AcOH, heat.
(iii) quinol.

and 257 corresponds to the loss of hydrobromous acid from the two isotopic parent ions.

The complicating effect of a methoxy-substituent in the 2-(2-nitrophenyl)-nucleus in the course of bromination already observed in the case of the ketone (32c) was also observed for the attempted bromination of the 1-(4-methoxyphenyl)-substituted ketone (24e). This compound reacted with bromine in 1,2-dimethoxyethane at room temperature to afford a complex mixture which gave no identifiable material. It is possible that the powerful electron-donating effect of the methoxy-substituent in the ketones (24e) and (32c) results in polybromination and hence the formation of the complex mixtures obtained.

In conjunction with the foregoing bromination studies the chlorination (Scheme 13) of 2-(2-nitrophenyl)-1-phenylethanone (24a) was also investigated as a route to the potential isatogen precursor 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64). The parent compound 1,2-diphenylethanone (24a; H for NO₂) is readily converted into 2-chloro-1,2-diphenylethanone (64; H for NO₂) by treatment with sulphuryl chloride.⁶⁵ The latter was therefore the reagent of choice for effecting the conversion [(24a) → (64)]. Initially the reaction of 2-(2-nitrophenyl)-1-phenylethanone (24a) with sulphuryl chloride was carried out in toluene at 40°. Under these conditions a substantial amount (54%) of the unreacted ketone (24a) was recovered. Also formed in

moderate yield (46%) was a product which gave analytical data and mass, i.r. and ^1H n.m.r. spectra consistent with its formulation as the previously unreported 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64). Significantly its ^1H n.m.r. spectrum lacked signals due to the protons of a methylene substituent but contained a one proton singlet at $\delta 7.10$ due to the hydrogen of a methine group which like that in the α -bromo-ketone (58a) (see before) is strongly deshielded by the combined electron-withdrawing effects of the adjacent chloro- and keto-groups. A very much improved yield (80%) of the α -chloro-ketone (64) was obtained by carrying out the chlorination of 2-(2-nitrophenyl)-1-phenylethanone (24a) in toluene at 40° in the presence of an equivalent amount of pyridine. The latter course improved the efficiency of the chlorination presumably by scavenging the acidic by-products (hydrogen chloride and sulphur dioxide).⁶⁵

2.4 Studies of Acid-catalysed Cyclisation Reactions of 1-Aryl-2-halogeno-2-(2-nitroaryl)ethanone Derivatives to 2-Aryl-3H-indol-3-one 1-N-oxides (2-Arylisatogens)

As had been discussed earlier (see page 45), Steel⁴⁸ showed that simply heating 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (58a) in glacial acetic acid resulted in its conversion in moderate yield (58%) into 5-bromo-2-phenylisatogen (62a). The development of practical synthetic

Table Ultraviolet spectra of 2-Aryl-3H-indol-3-one 1-N-oxides (2-Arylisatogens)*

Compound	ν_{\max} (nm)	$\log_{10} \epsilon_{\max}$	ν_{\max} (nm)	$\log_{10} \epsilon_{\max}$	ν_{\max} (nm)	$\log_{10} \epsilon_{\max}$	ν_{\max} (nm)	$\log_{10} \epsilon_{\max}$	ν_{\max} (nm)	$\log_{10} \epsilon_{\max}$
63a	204	(4.30)	279	(4.48)	286	(4.49)	442	(3.23)		
62b	205	(4.26)	222	(4.11)	281	(4.57)	462	(3.44)		
50a	205	(4.26)	283	(4.63)	281	(4.68)	454	(3.33)		
51a	212	(4.18)	280	(4.63)	288	(4.63)	446	(4.27)		
57	209	(4.16)	280	(4.61)	286	(4.63)	453	(3.35)		
62c	205	(4.31)	292	(4.65)	454	(3.44)				
51b	206	(4.41)	287	(4.64)	456	(3.43)				
50b	207	(4.17)	281	(4.60)	291	(4.63)	443	(3.29)		
63b	204	(4.29)	249	(4.05)	285	(4.60)	295	(4.04)	450	(3.27)
63c	206	(4.21)	219	(4.14)	282	(4.58)	291	(4.60)	452	(3.42)
63d	207	(2.19)	283	(4.62)	292	(4.64)	444	(3.42)		
62d	203	(4.19)	222	(4.16)	294	(4.31)	428	(3.53)		

(* measured for solutions in ethanol)

methods (Schemes 10-13) for the α -halogeno-ketones (45a and b), (52), (58b-d) and (64) meant it was now possible to investigate their potential as isatogen precursors. In practice, heating 2-bromo-2-(4-methyl-2-nitrophenyl)-1-phenylethanone (45a) under reflux in glacial acetic acid for three hours afforded a readily separated mixture of two products in good total yield (70%). The deep red colour of both products in conjunction with their analytical and spectroscopic properties allows the formulation of the major component (yield 55%) as the bromo-isatogen (50a) and the minor component (yield 15%) as the unbrominated isatogen (51a). Both compounds showed i.r. carbonyl absorption at ca. 1700 cm^{-1} and three fairly intense U.V. bands at ca. 210, 290 and 450 nm (Table) similar to 2-phenylisatogen (63a) (see later) and typical of 2-arylisatogens in general.⁶⁶ The ^1H n.m.r. spectrum of the bromoisatogen (50a) contains two one-proton singlets at δ 7.77 and 7.57 assignable to H-7 and H-4 respectively on the assumption that the N-oxide substituent will exert a greater deshielding effect than the carbonyl group at the 3-position. The appearance of the ^1H n.m.r. signals due to H-4 and H-7 as singlets established the 5-position as the site of the bromo-substituent in the bromoisatogen (50a).

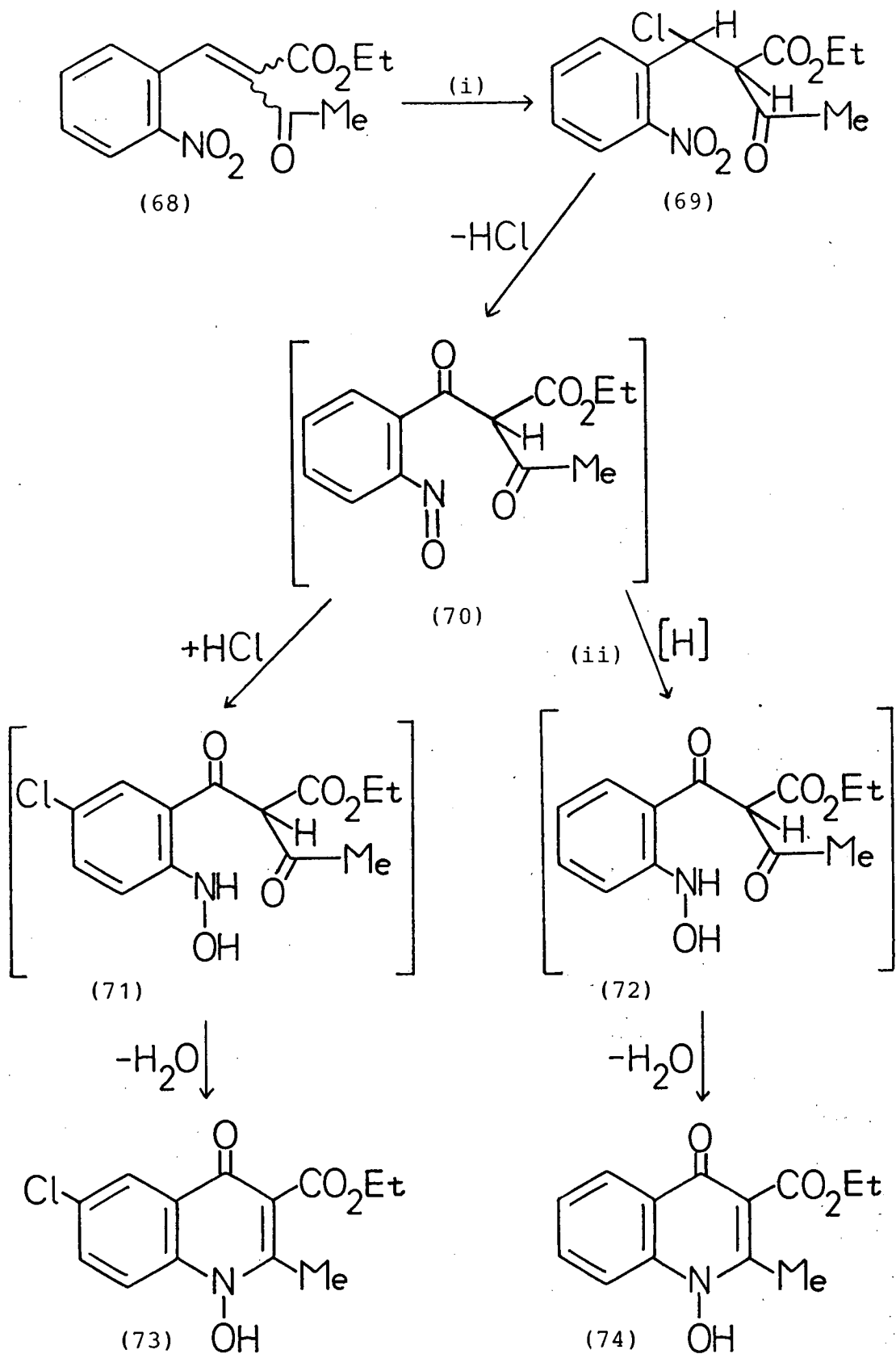
The formation of the unbrominated isatogen (51a) as well as the brominated isatogen (50a) from the bromo-ketone (45a) contrasts with the exclusive formation

(Scheme 1) of 5-bromo-2-phenylisatogen (5) from 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (1) observed by Steel.⁴⁸ This result can be readily explained (Scheme 10) by an extension of the mechanism (Scheme 1) already discussed (see page 45) to account for the transformation [(1) \rightarrow (5)]. Thus (Scheme 10), the transient nitroso intermediate (47a) derived from 2-bromo-2-(4-methyl-2-nitrophenyl)-1-phenylethanone (45a) will be more hindered at the 5-position, the site preferentially substituted by bromide ion en route to the brominated hydroxyamine precursor (48a) of the brominated isatogen (50a). This allows an alternative pathway (Scheme 10) to an isatogen product to intervene, involving direct reduction of the nitroso-intermediate (47a) by the hydrogen bromide present in the reaction mixture to give the unbrominated hydroxyamino-compound (49a) which subsequently cyclises and this accounts for the observed co-formation of the unbrominated isatogen (51a). These proposals are further substantiated by the behaviour (Scheme 10) of 2-bromo-2-(4-chloro-2-nitrophenyl)-1-phenylethanone (45b) when it is heated in glacial acetic acid for three hours as in the case of the methylated bromo-ketone (45a). This reaction afforded in addition to the large quantity (33%) of the unreacted starting-material (45b), a mixture which readily separated to give two products in yields of 11% and 24% whose orange/red colour and analytical and spectroscopic properties are fully consistent with the

isatogen structures (50b) and (51b) respectively. Both of these compounds showed i.r. carbonyl and U.V. absorption spectra (Table) similar to the methyl analogues (50a) and (51a). The 5-position for the bromo-substituent in the isatogen derivative (50b) is confirmed by the lack of splitting in the signals assignable to H-4 and H-7 in its ^1H n.m.r. spectrum. The disappointing result observed in the acid-catalysed cyclisation of the *chloro derivative* (45b) compared to the methyl derivative (45a) is consistent with the greater steric hindrance at the 5-position exerted by the bulkier chloro-substituent. The increased steric hindrance at the 5-position in going from the methyl-compound (45a) would also explain the greater formation of the unbrominated isatogen (51b) in the latter case. On the other hand steric inhibition of nucleophilic attack by the bromide ion at the 5-position as an explanation for the co-formation of the brominated and unbrominated isatogen products fails to explain the results obtained (Scheme 12) when the 2-bromo-1-(4-substituted aryl)-2-(2-nitrophenyl)-ethanones (58b-d) are heated in glacial acetic acid as for the bromo-ketones (45a and b). In each case these reactions provided good total yields (64-75%) of readily separated mixtures of the respective brominated and unbrominated isatogens (62b-d) and (63b-d) in which the former products predominated. The structures of the isatogen products (62b-d) and (63b-d) are consistent with the results obtained for their combustion analyses and spectroscopic

properties. In addition the known isatogen compounds (63c)^{25,18} and (63d)^{15,13} had melting-points in close agreement with the literature values. At present there is no explanation for the co-formation of the brominated and unbrominated isatogen products (62b-d) and (63b-d) in the acid-catalysed cyclisation reactions of the bromo-ketones (58b-d) beyond the operation of competing reaction pathways (see Scheme 12) for the conversion of transient nitroso-intermediates (59) into the hydroxyamino-precursors (60) and (61) of the isatogen products (62) and (63) with or without the incorporation of bromine in the 5-position.

In view of the apparent steric hindrance to the introduction of bromine at the 5-position observed in the cyclisation reactions of the bromoketones (45a and 45b) in glacial acetic acid, the result of the analogous reaction (Scheme 11) of 2-bromo-2-(5-methyl-2-nitrophenyl)-1-phenylethanone (52), where the 5-position is blocked by a methyl substituent, was of particular interest. The heating of the bromo-ketone (52) in glacial acetic acid under the standard conditions afforded none of the bromo-isatogen (56) derived by introduction of bromine at the 7-position instead of the blocked 5-position. The reaction instead yielded a large amount (52%) of unreacted starting-material (52) along with a low yield of a product which gave analytical data and showed the i.r., ¹H n.m.r. and U.V. (Table) absorption expected of the isatogen product (57). The



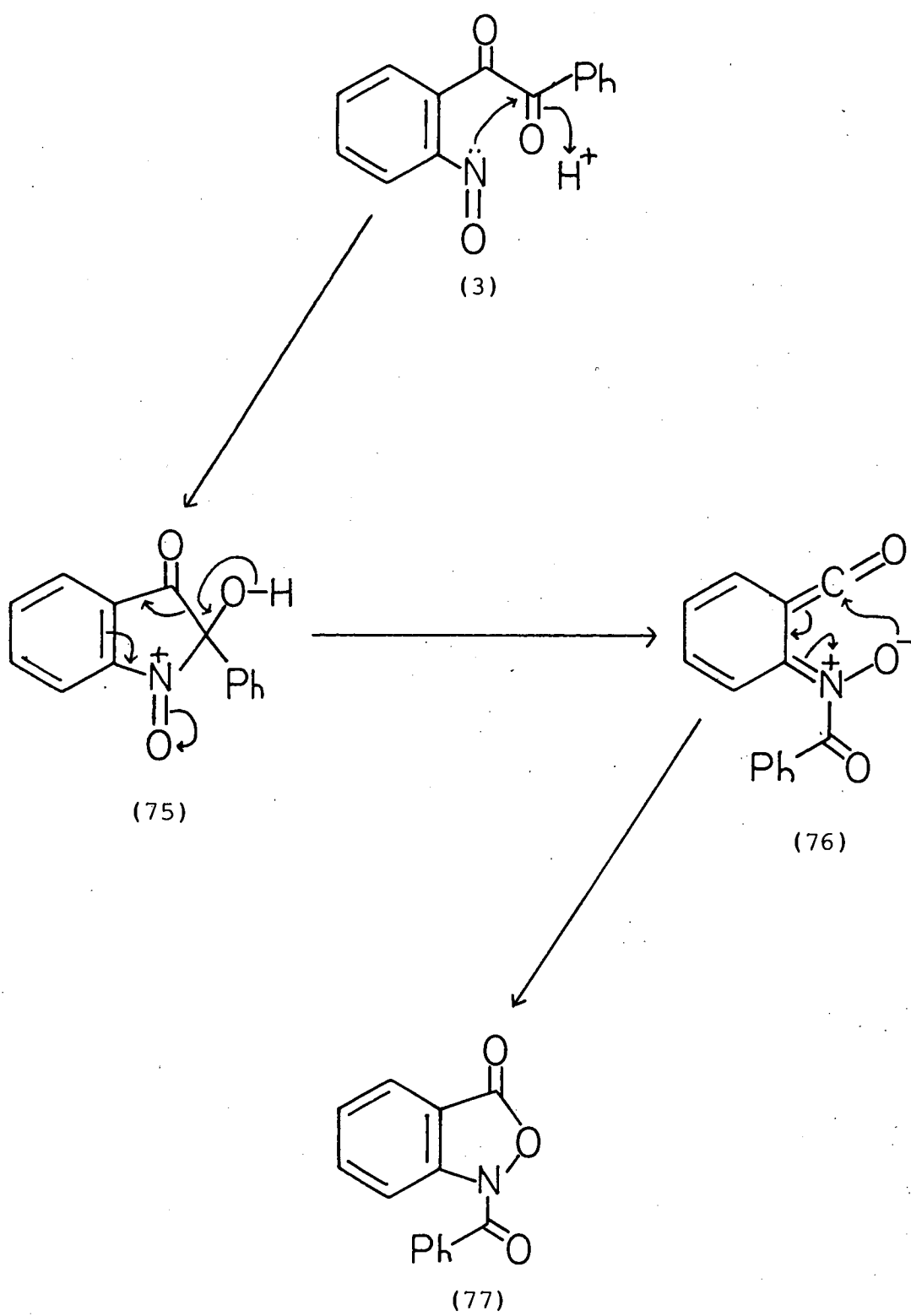
(i) HCl(g), diethyl ether, room temp.
(ii) quinol.

total lack of formation of a brominated isatogen product in the acid-catalysed cyclisation of 2-bromo-2-(5-methyl-2-nitrophenyl)-1-phenylethanone (52) is readily explained by the inability of the large bromide ion to substitute at the sterically hindered 3-position in the proposed nitroso-intermediate (53). The only isatogen product observed is that of the direct reduction pathway [(53) \rightarrow (55) \rightarrow (57)].

The apparent steric inhibition of bromine incorporation observed in the acid-catalysed cyclisation of the bromo-ketone (52) provides some support for the proposed mechanism (see Scheme 1) of such transformations. An analogous mechanism (Scheme 14) has been suggested⁶⁷ to account for the interesting hydrogen chloride catalysed cyclisation reactions of certain 2-nitrobenzylidene compounds [e.g. ethyl 2-nitrobenzylideneacetoacetate (68)] into chlorinated 1-hydroxy-2-quinolones [e.g. (73)]. These cyclisations are believed⁶⁷ to follow a pathway involving the initial formation of hydrogen chloride adducts [e.g. (69)] nitro-group side-chain participation in which logically affords, as also proposed for the isatogen cyclisation (see Scheme 1), transient 2-nitrosobenzoyl intermediates [e.g. (70)]. The latter are then converted with incorporation of chlorine into hydroxyamino-derivatives [e.g. (71)] dehydrative cyclisation of which affords the observed chlorinated N-hydroxy-2-quinolone products [e.g. (73)]. The indirect

support for the involvement of 2-nitrosobenzoyl intermediates [e.g. (70)] in such cyclisation reactions is provided by the formation⁶⁷ of chlorine-free products [e.g. (74)] when the cyclisation is carried out in the presence of quinol (hydroquinone). The latter provides an alternative reductive pathway to the quinolone product [e.g. (70) → (72) → (74)] without the accompanying incorporation of chlorine. It was therefore interesting to see if carrying out the cyclisation of 1-aryl-2-bromo-2-(2-nitroaryl)ethanones to 2-arylisatogens in glacial acetic acid in the presence of hydroquinone would result in the exclusive formation of bromine-free products thus enhancing the synthetic utility of these isatogen syntheses. In practice, the heating of 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (58a) in glacial acetic acid in the presence of hydroquinone afforded a low yield (36%) of a single isatogen product which was identified on the results of its melting point¹⁵ and its analytical and spectroscopic properties as the known¹³ 2-phenylisatogen (63a). The low yield of the reaction makes it impossible to draw any firm conclusions from the apparent lack of formation of 5-bromo-2-phenylisatogen (62a) though the relatively insoluble nature of this product should have ensured its ready isolation had it been present in the reaction mixture. In contrast to the behaviour of the parent bromo-ketone (58a), heating the 4-methyl derivative (45a) in glacial acetic acid in the

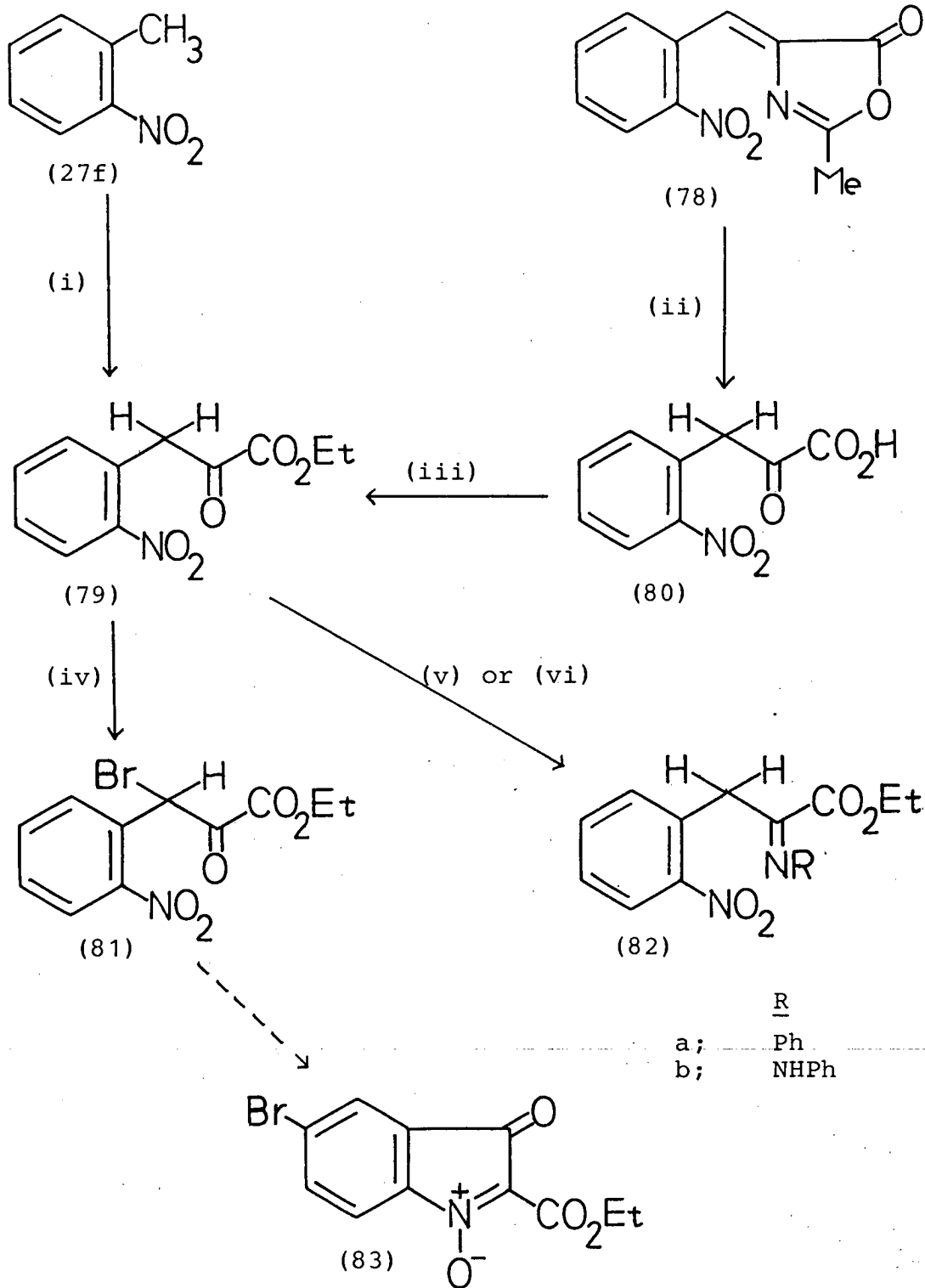
presence of hydroquinone resulted in its conversion in high total yield (84%) into the brominated and unbrominated isatogens (50a) and (51a) obtained before. The respective yields of the brominated product (50a) (11%) and the unbrominated product (51a) (73%) are essentially the reverse of those obtained in the absence of hydroquinone suggesting that the latter is tending to suppress halogen incorporation in the cyclisations of 2-bromo-2-(2-nitro-aryl)-1-arylethanones to 2-arylisatogens in glacial acetic acid. This is further substantiated by the finding that heating 2-bromo-2-(5-methyl-2-nitrophenyl)-1-phenylethanone (52) in glacial acetic acid in the presence of hydroquinone afforded a good yield (64%) of 5-methyl-2-phenylisatogen (57) with no evidence for the formation of the brominated product (56). This contrasts sharply with the high recovery of the starting-material (52) and the low yield of the unbrominated isatogen (57) obtained in the absence of hydroquinone (see before). The effect of adding hydroquinone in the course of the cyclisation reactions of 2-bromo-2-(2-nitroaryl)-1-arylethanones to 2-arylisatogens was not so clear-cut as in the hydrogen chloride catalysed cyclisations⁶⁷ of 2-nitrobenzylidene derivatives to 1-hydroxy-2-quinolones (Scheme 14) the trend was towards the suppression of halogen incorporation, and therefore supporting the mechanism for isatogen formation as outlined in Scheme 1. In conjunction with the foregoing



Scheme 15

studies the availability of the α -chloro-ketone (64) prompted the investigation of its behaviour towards heating under reflux in glacial acetic acid (Scheme 13). The expected product of this reaction was 5-chloro-2-phenylisatogen (67) but in practice a moderate yield of two products were obtained one of which (yield 50%) was shown by comparison with an authentic sample to be identical to benzoic acid. The second product (yield 21%) gave analytical and mass spectral data consistent with the molecular formula $C_{14}H_{19}NO_3$. Its 1H n.m.r. spectrum lacked signals other than those due to benzenoid protons. On the other hand, its i.r. spectrum contained bands at 1780 cm^{-1} and ca. 1690 cm^{-1} typical of the carbonyl residues present in γ -lactone and benzoyl substituents respectively. On the basis of this evidence and by comparison with an authentic sample,⁶⁸ the second product was identified (Scheme 15) as the known⁶⁹ compound 1-benzoyl-2,1-benzisoxazole (77). The mechanism of formation of this product from the α -chloro-ketone (64) is not clear but a tentative pathway originating in the nitroso-diketone intermediate (3) is outlined in Scheme 15. The transient nitroso-diketone (3) has also been proposed as the initial reaction intermediate in the acid-catalysed cyclisations of 2-bromo-2-(2-nitro-aryl)-1-arylethanones to 2-arylisatogens (see Scheme 1). In the absence of halogen acid (i.e. hydrogen chloride) this species (3) could undergo sequential ring-closure/ring opening reactions leading to the product (77) as shown in Scheme 15. If this proposal is correct the

formation of the 2,1-benzisoxazolone derivative (77) when the α -chloro-ketone (64) is heated in glacial acetic acid is due to the loss of the hydrogen chloride formed in the initial stage of the reaction [(64) \rightarrow (3)] before it has a chance to convert the nitroso-diketone (3) into the hydroxyamino-compound (65) and hence the isatogen (67). The validity of these assumptions was demonstrated by heating the α -chloro-ketone (64) under reflux in glacial acetic acid while simultaneously passing hydrogen chloride through the mixture. This reaction gave a high recovery (77%) of the starting-material (64) but also a low yield (22%) of a product which was identified as the previously unknown compound 5-chloro-2-phenylisatogen (67) on the basis of its combustion analysis and its mass, i.r. and ^1H n.m.r. spectra. The formation of the chloroisatogen (67) from the α -chloro-ketone (64) in the presence of excess hydrogen chloride can be rationalised (Scheme 13) by a pathway [(64) \rightarrow (3) \rightarrow (65) \rightarrow (67)] similar to that proposed (Scheme 1) for the related conversion of the α -bromo-ketone (1) into 5-bromo-2-phenylisatogen (5). In accord with the mechanism shown in Scheme 13, heating the α -chloro-ketone (64) in glacial acetic acid in the presence of hydroquinone afforded starting-material (49%) but also a low yield of 2-phenylisatogen (63a) which was found to be identical to an authentic sample (see before). The formation of this compound is readily explained by the ability of hydroquinone to promote an alternative reaction pathway to



- (i) $(\text{COOEt})_2$, KOEt, ether, 10° , then conc. H_2SO_4 , ether, room temp.
- (ii) dil. HCl, reflux.
- (iii) EtOH, conc. H_2SO_4 , heat.
- (iv) Br_2 , 1,2-dimethoxyethane, room temp.
- (v) PhNH_2 , 100° .
- (vi) PhNHNH_2 , EtOH, reflux.

product [(64) → (3) → (66) → (63a)] not involving the incorporation of chlorine.

2.5 An Attempted Extension of the Synthesis of 3H-Indol-3-one 1-N-oxides (Isatogens) from 2-Halogeno-2-(2-nitroaryl)ethanone Derivatives

In view of the general nature of the cyclisation reaction of 1-aryl-2-halogeno-2-(2-nitroaryl)ethanones to 2-arylisatogens in glacial acetic acid demonstrated by the foregoing studies, it was of interest to know if other 2-halogeno-2-(2-nitroaryl)ethanone derivatives would cyclise similarly to isatogens having substituents other than aryl at the 2-position. Such cyclisation reactions would expand considerably the practical methods available for isatogen synthesis (see Chapter 1). Thus (Scheme 16) by analogy with the ready acid-catalysed cyclisation reactions of 1-aryl-2-halogeno-2-(2-nitroaryl)ethanones to 2-arylisatogens described in Section 2.4, ethyl 3-bromo-3-(2-nitrophenyl)-2-oxopropanoate (81) could be expected to undergo cyclisation on heating in glacial acetic acid to afford ethyl 5-bromo-isatogen-2-carboxylate (83). The bromo-keto-ester (81) has been reported⁷⁰ only once in the literature as the bromination product of ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79). It was therefore decided to synthesise the bromo-keto-ester (81) and investigate its potential as a precursor of the isatogen derivative (83).

In practice the literature synthesis⁷⁰ of ethyl 3-(2-nitrophenyl)-2-oxopropanoate by the potassium ethoxide catalysed condensation of 2-nitrotoluene (27f) with diethyl oxalate yielded an oil and not the well defined solid (m.p. 69°) described by Wislicenus and Thoma.⁷⁰ However, the ¹H n.m.r. spectrum of this oil showed it to be a single product with characteristics entirely consistent with the structure (79). The oil obtained in the present studies was easily converted in good yield into the known⁷⁰ amide (79; CONH₂ for CO₂Et), N-phenylimine (82a) and phenylhydrazone (82b) derivatives all of which had melting points consistent with the literature values.⁷⁰ In addition, the oil could be sequentially hydrolysed and cleaved by hydrogen peroxide to give 2-nitrophenylacetic acid in good yield.

The accumulated evidence indicates that the oil is ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) despite its description as a solid by Wislicenus and Thoma.⁷⁰ However, to ensure the identity of the oil as ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) it was decided to synthesise this compound by an alternative route. Since the acylation (Scheme 8) of the enamine (38f) followed by hydrolysis had been useful for the synthesis of the 1-aryl-2-(2-nitrophenyl)ethanones (32), an attempt was made to synthesise ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) by acylation of the enamine (38f) with ethoxalyl chloride (EtO₂C.COCl)

followed by hydrolysis. This reaction disappointingly gave only a small amount of unreacted 2-nitrotoluene (27f) and a series of complex oils and gums from which no identifiable material could be obtained. It was next decided to synthesise the α -keto-ester (79) by the more orthodox method of esterifying 3-(2-nitrophenyl)-2-oxopropanoic acid (80). The latter compound was readily synthesised in good overall yield by the method of Johnson, Hasbrouk and Dutcher⁷¹ involving the condensation of 2-nitrobenzaldehyde with N-acetylglycine to afford the 2-nitrobenzylideneoxazolinone derivative (78) with subsequent hydrolysis of the latter with hydrochloric acid. The α -keto-acid obtained was then smoothly esterified in good yield (80%) by treatment with ethanol in the presence of concentrated sulphuric acid to afford ethyl 3-(2-nitrophenyl)-2-oxopropionate (79) as an oil identical to that obtained previously by the potassium ethoxide catalysed condensation of 2-nitrotoluene (27f) with diethyl oxalate.

Now that the identity of the oil had been definitely established as ethyl 3-(2-nitrophenyl)-2-oxopropionate (79) its conversion into the required bromo-derivative (81) was attempted. Ethyl 3-bromo-3-(2-nitrophenyl)-2-oxopropionate (81) is reported in the literature as a solid (m.p. 82°) obtained by Wislicenus and Thoma⁷⁰ by the bromination of the α -keto-ester (79). The reaction of the oil believed to be ethyl 3-(2-nitrophenyl)-2-oxopropionate (79) with

bromine in 1,2-dimethoxyethane at room temperature afforded a single component oil whose i.r. and ^1H n.m.r. spectra were consistent with it being the required bromo-derivative (81). However, in view of the description of the latter as a well-defined solid by Wislicenus and Thoma⁷⁰ and the lack of time, the proposed cyclisation of the oily bromination product obtained to the isatogen derivative (83) was not attempted. Further investigation by others in the future will be required to firmly resolve the problems of the nature of the α -keto-ester (79) and its bromination product (81). It will then be possible to investigate the acid-catalysed cyclisation of the latter to the isatogenic ester (83).

2.6 Experimental

2-Nitrophenylacetyl Chloride (23)

2-Nitrophenylacetyl chloride (23) was prepared by the reaction of 2-nitrophenylacetic acid (22) with thionyl chloride as described in the literature,⁵⁶ and was obtained as an amber oil (yield quant.) which due to its thermal instability, was used without purification.

2-(2-Nitrophenyl)-1-phenylethanone (24a)

2-(2-Nitrophenyl)-1-phenylethanone (24a) was prepared by the reaction of 2-nitrophenylacetyl chloride (23) with benzene in the presence of aluminium trichloride as described by Steel⁴⁸ (yield 64%), m.p. 76° (lit.⁴⁸, 81°) and was further characterised by its reaction with hydroxylamine to give the oxime (yield 96%), m.p. 118° (lit.⁴⁸, 118°).

2-(2-Nitrophenyl)-1-phenylethanone Azine (26)

A solution of 2-(2-nitrophenyl)-1-phenylethanone (24a) (0.48 g; 0.002 mol) in ethanol (20.0 ml) was treated with hydrazine hydrochloride (0.84 g; 0.008 mol) and the mixture was heated under reflux for 19 h. The resulting clear solution was evaporated to afford a yellow solid which was dissolved in methylene chloride (20.0 ml) and the solution washed with water (2 x 20.0 ml) and evaporated to afford an oily solid (0.46 g). This was crystallised to give 2-(2-nitrophenyl)-1-phenylethanone azine (26)

(0.14 g; 29%) which formed yellow crystals, m.p. 179° (from toluene-light petroleum), ν_{\max} 1520 and 1340 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.00-7.65 (6H, m, ArH), 7.50-7.00 (12H, m, ArH) and 4.73 (4H, s, CH_2).

Found: C, 70.7; H, 4.6; M, 11.6%; M^+ , 478.

$\text{C}_{28}\text{H}_{22}\text{N}_4\text{O}_4$ requires: C, 70.3; H, 4.6; M, 11.7%; M^+ , 478.

The filtrate was evaporated to afford unreacted 2-(2-nitrophenyl)-1-phenylethanone (24a) (0.28 g; 58%), m.p. 74° (lit.,⁴⁸ 81°) identical (i.r. spectrum) to an authentic sample.

2-(2-Nitrophenyl)-1-phenylethanone Toluene-4-sulphonylhydrazone (25)

A solution of 2-(2-nitrophenyl)-1-phenylethanone (24a) (0.48 g; 0.002 mol) in methanol (15.0 ml) was treated with toluene-4-sulphonylhydrazine (0.37 g; 0.002 mol) and the mixture was heated under reflux for 15 h. The resulting clear solution was evaporated to yield a yellow solid which was crystallised to afford 2-(2-nitrophenyl)-1-phenylethanone toluene-4-sulphonylhydrazone (25) (0.56 g; 68%) as colourless crystals, m.p. 147° (from toluene), ν_{\max} 3190 (NH) and 1520 and 1350 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.09-7.11 (14H, m, ArH and NH), 4.11 (2H, s, CH_2) and 2.44 (3H, s, CH_3)

Found: C, 61.7; H, 4.6; N, 10.2%; M^+ , 409.

$\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$ requires: C, 61.6; H, 4.7; N, 10.3%; M, 409.

1,4-Dimethyl-2-nitrobenzene (27a)

1,4-Dimethyl-2-nitrobenzene (27a) was prepared by the reaction of 1,4-dimethylbenzene with fuming nitric acid as described by Snyder and Pilgrim⁵⁹, (yield 85%), b.p. 60-72°/0.2 mmHg (lit.⁵⁹, 64-65°/0.35 mmHg).

Syntheses of 3-(2-Nitroaryl)-2-oxopropanoic Acids (29)

(a) By the sodium ethoxide catalysed condensation of 2-nitrotoluene derivatives with diethyl oxalate

A solution of sodium (5.8 g; 0.25 g. atom) in anhydrous ethanol (250 ml) was evaporated under anhydrous conditions and the remaining ethanol was removed by azeotropic distillation with anhydrous toluene. The residual solid sodium ethoxide was suspended in anhydrous ether (150 ml) and the suspension was stirred and treated dropwise at room temperature with the exclusion of atmospheric moisture with diethyl oxalate (29.2 g; 0.20 mol) at a rate sufficient to cause gentle reflux. The mixture was stirred for 5 min. then treated dropwise with a solution of the corresponding 2-nitrotoluene derivative (27) (0.15 mol) in anhydrous diethyl ether (50.0 ml) and the mixture heated under reflux for 18 h. The solution was cooled, treated with 5% w/v aqueous sodium hydroxide solution (250 ml) and the mixture stirred vigorously at room temperature for 0.5 h. The mixture was acidified

with concentrated hydrochloric acid and the resulting two-phase system was separated and the aqueous layer extracted with ether (2 x 500 ml) and rejected.

The combined ether-extracts were washed with 5% w/v aqueous sodium hydroxide solution (4 x 50.0 ml) and the combined alkaline extracts acidified with concentrated hydrochloric acid and extracted with ether (4 x 60.0 ml) to give a brown semi-solid which was triturated with toluene and the brown solid collected to afford the corresponding 3-(2-nitrophenyl)-2-oxopropanoic acid (29).

(i) 5-Methoxy-2-nitrotoluene (27d) gave 3-(5-methoxy-2-nitrophenyl)-2-oxopropanoic acid (29c) (yield 63%), m.p. 126° (lit.⁵⁸, 125°) ν_{\max} 1725 br (CO) and 1500 and 1340 (NO₂) cm⁻¹.

(ii) 1,3-Dimethyl-4-nitrobenzene (27b) gave 3-(5-methyl-2-nitrophenyl)-2-oxopropanoic acid (29b) (yield 70%), m.p. 142° (lit.⁵⁷, 193°), ν_{\max} 3430 (OH), 1735 and 1700 (CO) and 1510 and 1340 (NO₂) cm⁻¹.

Found: M⁺, 223.

C₁₀H₉NO₅ requires: M, 223.

(iii) 1,4-Dimethyl-2-nitrobenzene (27a) gave 3-(4-methyl-2-nitrophenyl)-2-oxopropanoic acid (29a) (yield 39%) m.p. 135° (lit.⁵⁹, 147°) ν_{\max} 3350 br (OH), 1680 br (CO) and 1520 and 1360 (NO₂) cm⁻¹.

The toluene filtrate was evaporated to afford a brown oil (9.2 g) whose t.l.c. in ethyl acetate-methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

(b) By the potassium ethoxide catalysed condensation of 2-nitrotoluene derivatives with diethyl oxalate

A solution of potassium (4.1 g; 0.10 g.atom) in anhydrous ethanol (30.0 ml) was stirred and treated at room temperature with the exclusion of atmospheric moisture with anhydrous diethyl ether (150 ml) then with a single portion of diethyl oxalate (14.6 g; 0.10 mol) followed by the corresponding 2-nitrotoluene derivative (27) (0.10 mol). The resulting red solution was stirred and heated under reflux (steam bath) for 5 h. and the mixture was then cooled and filtered to obtain the potassium enolate (28) of the corresponding ethyl 3-(2-nitroaryl)-2-oxopropanoate which was washed with a little anhydrous ether and sucked dry, then reacted further, as described for the individual reactions below.

(i) 2-Chloro-6-nitrotoluene (33) (17.2g; 0.10 mol) gave the red potassium enolate of ethyl 3-(2-chloro-6-nitrophenyl)-2-oxopropanoate and an ethereal filtrate which was evaporated to yield an oil whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multi-component mixture which was not further investigated.

The red crystalline enolate was dissolved in water (200 ml) and the solution was stirred vigorously at room temperature for 4 h. then treated with 2M aqueous hydrochloric acid solution to give a two phase system which was extracted with methylene chloride (3 x 20 ml) to give a brown oil (15.6 g). On standing the oil partially solidified and was triturated with toluene to give 3-(2-chloro-6-nitrophenyl)-2-oxopropanoic acid (34) (10.3 g; 42%), m.p. 102° (lit.⁶⁰, 114°) ν_{\max} 3390 (OH), 1765 and 1735 (CO) and 1530 and 1310 (NO₂) cm⁻¹.

The toluene mother liquor was evaporated to give an oil (3.8 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(ii) 1,3-Dimethyl-4-nitrobenzene (27b) (15.2g; 0.10 mol) gave the red potassium enolate of ethyl 3-(5-methyl-2-nitrophenyl)-2-oxopropanoate (28b) (16.7 g; 58%) [83% based on unrecovered 1,3-dimethyl-4-nitrobenzene (27b)] and an ethereal filtrate which was evaporated to afford a semi-solid (10.8 g) that was flash-chromatographed over silica to give unreacted 1,3-dimethyl-4-nitrobenzene (27b) as an oil (4.6 g; 30%) identified by comparison (t.l.c. and i.r. spectrum) with an authentic sample.

A solution of the potassium enolate of ethyl 3-(5-methyl-2-nitrophenyl)-2-oxopropanoate (28b) (16.7g; 0.057 mol)

in water (200 ml) was stirred at room temperature for 4 h. and filtered to remove a little insoluble material. The aqueous filtrate was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to give 3-(5-methyl-2-nitrophenyl)-2-oxopropanoic acid (29b) (11.8 g; 93%), m.p. 143° (lit.⁵⁷, 193°), identical (i.r. spectrum) to a sample prepared before.

Synthesis of 2-Nitroarylacetic Acids (30)

(a) By the Sodium Ethoxide Catalysed Condensation of 2-Nitrotoluene Derivatives with Diethyl Oxalate Followed by Hydrolysis and Oxidation with Hydrogen Peroxide

A solution of sodium (2.3 g; 0.1 g.atom) in methanol (100 ml) was evaporated and the residual solid sodium methoxide was treated with the corresponding 2-nitrotoluene derivative (0.1 mol) and diethyl oxalate (0.1 mol) and the mixture heated under reflux for 1 h. The mixture was cooled, treated with water (70 ml) and the mixture heated under reflux for a further 1 h. The solution was concentrated to remove the ethanol and the aqueous mother liquor was extracted with methylene chloride to give an oil. The oil and the aqueous mother liquor were worked up as described for the individual reactions below.

(i) The oil (12.7 g) from 1,3-dimethyl-4-nitrobenzene (27b) (15.1 g; 0.1 mol) was shown by t.l.c. in ether over silica to be an unresolvable multicomponent mixture which was not further investigated.

The aqueous mother liquor was treated with 30% w/v aqueous hydrogen peroxide solution (96.0 g; 86.5 ml) and the mixture was stirred at 30-35° (water bath) for 30 min. then acidified with 2M aqueous hydrochloric acid. The resulting suspension was extracted with methylene chloride and evaporated to give a yellow solid (1.5 g) m.p. 108° whose t.l.c. in ether over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(ii) The oil (16.6 g) from 3-methyl-4-nitroanisole (27c) (16.7 g; 0.1 mol) was dissolved in ether and the solution decanted from a small quantity of gum and evaporated to obtain a dark solid which was collected with the aid of a little ether to afford unreacted 3-methyl-4-nitroanisole (27c) (7.9 g; 47%) m.p. 47°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was stirred and treated with 30% w/v aqueous hydrogen peroxide solution (96.0 g; 86.5 ml) at 30-35° (water bath) and the mixture was stirred at this temperature for 30 min. The solution was acidified with 2M aqueous hydrochloric acid and the

precipitated brown solid was collected, washed with water and dried in vacuo to give 5-methoxy-2-nitrophenylacetic acid (30c) (1.4 g; 7%) [13% based on unrecovered 3-methyl-4-nitroanisole (27c)], m.p. 175° (lit.⁵⁸, 176°) ν_{\max} 1715 (CO) and 1515 and 1340 (NO_2) cm^{-1} .

(b) By the oxidation of 3-(2-nitroaryl)-2-oxopropanoic acids with hydrogen peroxide

A red solution of the corresponding 3-(2-nitroaryl)-2-oxopropanoic acid (29) (0.15 mol) in 2% w/v aqueous sodium hydroxide (287 ml) was stirred, cooled to 10° (ice-bath) and treated dropwise with 6% aqueous hydrogen peroxide solution (598 ml) until the red colour was discharged. The mixture evolved carbon dioxide and was stirred at room temperature for 1 h. The resulting yellow brown solution was acidified with 2M aqueous hydrochloric acid and the precipitated solid was collected to give the corresponding 2-nitrophenylacetic acid (30).

(i) The oxidation of 3-(4-methyl-2-nitrophenyl)-2-oxopropanoic acid (29a) gave 4-methyl-2-nitrophenylacetic acid (30a) (yield 92%) m.p. 167° (lit.⁶¹, 172°), ν_{\max} 1695 (CO) and 1535 and 1345 (NO_2) cm^{-1} .

Extraction of the aqueous acidic mother liquor with methylene chloride gave no further identifiable material.

(ii) The oxidation of 3-(5-methyl-2-nitrophenyl)-2-oxopropanoic acid (29b) afforded a solid which was combined with further material obtained by extracting the aqueous mother liquor with methylene chloride to afford 5-methyl-2-nitrophenylacetic acid (30b) (total yield 63%) m.p. 127° (lit.,^{57,62} 149°), ν_{\max} 1695 (CO) and 1515 and 1340 (NO_2) cm^{-1} .

Found: M^+ , 195.

$\text{C}_9\text{H}_9\text{NO}_4$ requires: M, 195.

(iii) The oxidation of 3-(5-methoxy-2-nitrophenyl)-2-oxopropanoic acid (29c) gave 5-methoxy-2-nitrophenylacetic acid (30c) (yield 93%) m.p. 176° (lit.⁵⁸, 176°), ν_{\max} 1720 (CO) and 1505 and 1340 (NO_2) cm^{-1} .

Extraction of the aqueous acidic filtrate with methylene chloride gave only a small amount of intractable brown gum (0.32 g) which was not further investigated.

(iv) The oxidation of 3-(2-chloro-6-nitrophenyl)-2-oxopropanoic acid (34) gave 2-chloro-6-nitrophenylacetic acid (35) (yield 87%) m.p. 193° (lit.⁶⁰, 193°) ν_{\max} 1710 (CO) and 1525 and 1350 (NO_2) cm^{-1} .

Extraction of the acidic aqueous mother liquor with methylene chloride gave no further identifiable material.

Syntheses of Substituted Benzoyl Chlorides (4l)

(a) Substituted benzoyl chlorides were prepared by the reaction of the corresponding benzoic acids with thionyl chloride as described in the literature⁷² and were purified by high vacuum distillation.

(i) 4-Methylbenzoic acid gave 4-methylbenzoyl chloride (4lb) (yield 71%) b.p. 70°/2 mmHg (lit.⁷³, 102°/15 mmHg).

(ii) 4-Methoxybenzoic acid afforded 4-methoxybenzoyl chloride (4le) (yield 94%) m.p. 24° (lit.⁷³, m.p. 22°).

(iii) 4-Chlorobenzoic acid gave 4-chlorobenzoyl chloride (4lc) (yield 65%), b.p. 90°/6.5 mmHg (lit.⁷³, 110°/18 mmHg).

(b) 4-Nitrobenzoyl chloride (4ld) was provided by Mr. R. McGuire and was prepared by the reaction of 4-nitrobenzoic acid with phosphorus pentachloride as described in the literature, and had m.p. 71° (lit.⁷⁴, 73°).

Syntheses of 2-(2-Nitroaryl)-1-arylethanones (32)

(a) By Friedel-Crafts reactions of 2-nitroaryl-acetyl chlorides (31) with benzene derivatives

A vigorously stirred suspension of the corresponding 2-nitroarylacetic acid (30) (0.09 mol) in the appropriate anhydrous benzene derivative (47.0 ml) was cooled to 10-15°

(ice-water bath) and treated dropwise with thionyl chloride (11.9 g; 0.1 mol) then stirred and heated at 45° (water bath) for 4 h. to give a brown solution of the substituted 2-nitroarylacetyl chloride (31). This was added dropwise at 10-20° (water bath) with exclusion of atmospheric moisture to a vigorously stirred suspension of aluminium trichloride (14.7 g; 0.11 mol) in the corresponding anhydrous benzene derivative (135 ml). The mixture was stirred and heated gradually to the reflux temperature over 1.5 h. and then heated under reflux for 1 h. The mixture was cooled, poured into a mixture of ice and 2M aqueous hydrochloric acid (225 ml), filtered to remove inorganic material and the two phase filtrate worked up as described for the individual reactions below.

(i) The two phase filtrate from the Friedel-Crafts reaction of 4-methyl-2-nitrophenylacetyl chloride (31a) with benzene was separated and the aqueous layer was washed with benzene (2 x 50.0 ml). Evaporation of the combined benzene extracts gave a gummy brown solid (21.0 g) which was dissolved in methylene chloride and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution and water and evaporated to give a brown solid. This was purified by crystallisation to afford 2-(4-methyl-2-nitrophenyl)-1-phenylethanone (32a) (45%) [50% based on unrecovered 4-methyl-2-nitrophenylacetic acid (30a)] which formed

colourless crystals m.p. 120° (from toluene), ν_{\max} 1675 (CO) and 1525 and 1340 (NO_2) cm^{-1} , δ_{H} 8.09-7.97 (3H, m, ArH), 7.62-7.16 (5H, m, ArH), 4.67 (2H, s, CH_2), and 2.45 (3H, s, CH_3).

Found: C, 70.4; H, 5.1; N, 5.4%; M^+ , 255.

$\text{C}_{15}\text{H}_{13}\text{NO}_3$ requires: C, 70.6; H, 5.1; N, 5.5%; M, 255.

Evaporation of the toluene mother liquor yielded a dark red gum (6.8 g) whose t.l.c. in methylene chloride-light petroleum over silica showed it to be a close-running multicomponent mixture which was not further investigated.

The combined aqueous sodium hydrogen carbonate and aqueous washings were acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to yield unreacted 4-methyl-2-nitrophenylacetic acid (30a) (9%) m.p. 166° (lit.⁶¹, 169°), identical (i.r. spectrum) to an authentic sample prepared before.

(ii) The two phase filtrate from the Friedel-Crafts reaction of 5-methoxy-2-nitrophenylacetyl chloride (31c) with benzene was separated and the aqueous layer was extracted with benzene (4 x 25.0 ml). Evaporation of the combined benzene extracts gave a brown oil (3.3 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

(iii) The two phase filtrate from the Friedel-Crafts reaction of 2-chloro-6-nitrophenylacetyl chloride (36) with benzene was separated and the aqueous layer was washed with benzene (3 x 20.0 ml) and the combined benzene extracts evaporated to afford an oily solid. This was dissolved in methylene chloride (30.0 ml) and the solution was washed with 10% w/v aqueous sodium hydrogen carbonate solution and water and evaporated to obtain 2-(2-chloro-6-nitrophenyl)-1-phenylethanone (37) (22%) [41% based on unrecovered 2-chloro-6-nitrophenylacetic acid (35)] which formed colourless crystals, m.p. 190° (from diethyl ether), ν_{\max} 1680 (CO) and 1525 and 1350 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.12-7.92 (3H, m, ArH), 7.78-7.25 (5H, m, ArH) and 4.89 (2H, s, CH_2).

Found: C, 61.3; H, 3.8; N, 5.2%; M^+ , 277 and 275.

$\text{C}_{14}\text{H}_{10}\text{ClNO}_3$ requires: C, 61.0; H, 3.6; N, 5.1%; M, 275.5.

The combined aqueous sodium hydrogen carbonate mother liquor and aqueous washings were acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to afford unreacted 2-chloro-6-nitrophenylacetic acid (35) (46%) m.p. 190° (lit.⁶⁰, 193°) identical (i.r. spectrum) to an authentic sample.

(iv) The two phase filtrate from the Friedel-Crafts reaction of 2-nitrophenylacetyl chloride (23) with toluene was separated and the aqueous layer was extracted with toluene (2 x 50.0 ml). Evaporation of the combined toluene

extracts gave a dark brown oil which was flash chromatographed over silica.

Elution with light petroleum-ethyl acetate (3:1) afforded 1-(4-methylphenyl)-2-(2-nitrophenyl)ethanone (24b) (25%) which formed light brown crystals m.p. 77° (from toluene), ν_{\max} 1675 (CO) and 1520 and 1355 (NO₂) cm⁻¹, δ_{H} (CDCl₃) 8.19-8.07 (1H, m, ArH), 7.93 (2H, d, J 8Hz; ArH), 7.62-7.38 (3H, m, ArH), 7.30 (2H, d, J 8Hz, ArH), 4.69 (2H, s, CH₂) and 2.43 (3H, s, CH₃).

Found: C, 70.4; H, 5.0; N, 5.5%; M⁺, 255.

C₁₅H₁₃NO₃ requires: C, 70.6; H, 5.1; N, 5.5%; M, 255.

Further elution with light petroleum-ethyl acetate (3:1) and ethanol gave only intractable gums and oils from which no identifiable material could be obtained.

(b) By reaction of 2-nitrotoluene derivatives (27) with dimethylformamide dimethyl acetal and in situ triethylamine catalysed condensation of the resulting 1-(N,N-dimethylamino)-2-(2-nitroaryl)ethenes (38) with aroyl chlorides (41) followed by hydrolysis^{52,53}

A solution of the corresponding 2-nitrotoluene derivative (27) (0.025 mol) in anhydrous dimethylformamide (10.0 ml) was stirred and treated dropwise with dimethylformamide dimethyl acetal (3.3 g; 0.028 mol) and the mixture was heated under reflux with the exclusion of atmospheric moisture for 26 h.

The dimethylformamide was removed from the resulting red solution by distillation under reduced pressure at 80°/2 mmHg to afford the corresponding 1-(N,N-dimethylamino)-2-(2-nitro-aryl)ethene (38) as a viscous red oil. This was dissolved in anhydrous toluene (25.0 ml) and the solution treated dropwise with stirring with triethylamine (2.5 g, 0.025 mol) followed by the appropriate aroyl chloride (41) (0.025 mol). The mixture was stirred and heated under reflux with the exclusion of atmospheric moisture for 15 h., then worked up as described for the individual reactions below.

(i) The mixture from the condensation of 2-nitrotoluene (27f) with dimethylformamide dimethyl acetal then reaction with benzoyl chloride (41a) was cooled, treated with water (25.0 ml) and the two-phase mixture obtained separated and the organic phase evaporated to give a brown oil. This was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture was heated under reflux for 18 h. The resulting brown solution was evaporated to afford a brown oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to yield a brown oil. This was flash-chromatographed over silica.

Elution with toluene gave unreacted 2-nitrotoluene (27f) as an oil (16%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Elution with methylene chloride afforded 2-(2-nitrophenyl)-1-phenylethanone (32f) (25%) [30% based on unrecovered 2-nitrotoluene (27f)] m.p. 71° (lit.⁴⁸, 81°) identical (t.l.c. and i.r. spectrum) to an authentic sample prepared before.

Further elution with ethyl acetate yielded only a brown oil whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(ii) The mixture from the condensation of 1,4-dimethyl-2-nitrobenzene (27a) with dimethylformamide dimethyl acetal

then reaction with benzoyl chloride (41a) was cooled, treated with water (25.0 ml) and the two-phase mixture obtained separated and the organic phase evaporated to afford a brown oil. This was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture was heated under reflux for 18 h. The resulting solution was evaporated to give a red oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) then water (2 x 10.0 ml). Evaporation of the methylene chloride extract gave a brown gummy solid which was flash-chromatographed over silica.

Elution with toluene yielded unreacted 1,4-dimethyl-2-nitrobenzene (27a) as an oil (45%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with toluene afforded a small amount of an intractable gummy solid from which no identifiable material could be obtained.

Further elution with toluene then methylene chloride gave 2-(4-methyl-2-nitrophenyl)-1-phenylethanone (32a) (46%) [83% based on unrecovered 1,4-dimethyl-2-nitrobenzene (27a)] m.p. 118° identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Subsequent elution with ethyl acetate through to methanol gave intractable oils whose t.l.c. in ethyl acetate-light petroleum over silica showed them to be close-running multicomponent mixtures which were not further investigated.

(iii) The mixture from the condensation of 1,3-dimethyl-4-nitrobenzene (27b) with dimethylformamide dimethyl acetal then reaction with benzoyl chloride (41a) was cooled and treated with water (25.0 ml). The toluene layer was separated and evaporated to give a brown oil which was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the solution heated under reflux for 18 h. The mixture was evaporated and the resulting brown oil was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml). Evaporation of the methylene chloride extract gave a brown oil which was flash-chromatographed over silica.

Elution with toluene afforded unreacted 1,3-dimethyl-4-nitrobenzene (27b) as an oil (42%), identical (t.l.c. and i.r. spectrum) to an authentic sample.

Elution with toluene-methylene chloride (1:1) yielded 2-(5-methyl-2-nitrophenyl)-1-phenylethanone (32b) (35%) [49% based on unrecovered 1,3-dimethyl-4-nitrobenzene (27b)] which formed colourless crystals, m.p. 107° (from toluene), ν_{\max} 1685 (CO) and 1510 and 1345 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.13-7.97 (3H, m, ArH), 7.63-7.14 (5H, m, ArH), 4.68 (2H, s, CH_2) and 2.43 (3H, s, CH_3).

Found: C, 71.1; H, 5.2; N, 5.5%; M^+ , 255.

$\text{C}_{15}\text{H}_{13}\text{NO}_3$ requires: C, 70.6; H, 5.1; N, 5.5%; M, 255.

Found: M^+ , 255.0890

$\text{C}_{15}\text{H}_{13}\text{NO}_3$ requires: M, 255.0895.

Elution with methylene chloride through to methanol gave only intractable gums and oils whose t.l.c. in methylene chloride over silica showed them to be multicomponent mixtures which were not further investigated.

(iv) The mixture from the condensation of 3-methyl-4-nitroanisole (27c) with dimethylformamide dimethyl acetal then reaction with benzoyl chloride (41a) was cooled, treated with water (25.0 ml) and filtered to afford 1-benzoyl-2-(N,N-dimethylamino)-1-(5-methoxy-2-nitrophenyl)ethene (39d)

(47%) which formed red crystals m.p. 151° (from toluene), ν_{\max} 1630 (CO) and 1505 and 1335 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.10-6.74 (9H, m, CH and ArH), 3.87 (3H, s, OCH_3) and 2.75 [6H, s, $\text{N}(\text{CH}_3)_2$].

Found: C, 66.5; H, 5.6; N, 8.6%; M^+ , 326.

$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$ requires: C, 66.3; H, 5.5; N, 8.6%; M, 326.

The two-phase mother liquor was separated and the organic layer was evaporated to give an oil which was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture heated under reflux for 18 h. The mixture was cooled and evaporated to give a brown oil. This was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to yield a brown gummy solid which was flash-chromatographed over silica.

Elution with toluene gave unreacted 3-methyl-4-nitroanisole (27c) (7%) m.p. 51° identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Elution with methylene chloride yielded 2-(5-methoxy-2-nitrophenyl)-1-phenylethanone (32c) (39%) [53% based on unrecovered 3-methyl-4-nitroanisole (27c)] m.p. 130° identical (m.p. and i.r. spectrum) to an authentic sample prepared later.

Further elution with ethyl acetate through to methanol gave only oils and glasses from which no identifiable material could be obtained.

(v) The mixture from the condensation of 4-chloro-2-nitrotoluene (27d) with dimethylformamide dimethyl acetal then reaction with benzoyl chloride (41a) was cooled and treated with water (25.0 ml). The resulting three phase mixture was filtered to remove a small amount of unidentified solid, and the toluene layer was separated from the two phase filtrate and evaporated to afford a brown oil. This was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture heated under reflux for 18 h. The resulting brown solution was evaporated and the oil obtained dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to yield a brown oil which was flash-chromatographed over silica.

Elution with toluene afforded unreacted 4-chloro-2-nitrotoluene (27d) as an oil (28%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with toluene yielded 2-(4-chloro-2-nitrophenyl)-1-phenylethanone (32d) (21%) [29% based on unrecovered 4-chloro-2-nitrotoluene (27d)] which formed colourless crystals m.p. 119° (from toluene), ν_{\max} 1680 (CO) and 1530 and 1350 (NO₂) cm⁻¹, δ_{H} (CDCl₃) 8.16-7.96 (3H, m,

ArH), 7.65-7.23 (5H, m, ArH) and 4.69 (2H, s, CH₂).

Found: C, 61.2; H, 3.5; N, 5.1%; M⁺, 277 and 275.

C₁₄H₁₀ClNO₃ requires: C, 61.0; H, 3.6; N, 5.1%; M, 275.5.

Elution with toluene through methylene chloride and ethyl acetate to methanol gave only gums (total 3.8 g) whose t.l.c. in toluene over silica showed them to be complex mixtures which were not further investigated.

(vi) The mixture from the condensation of 2-chloro-6-nitrotoluene (33) with dimethylformamide dimethyl acetal then reaction with benzoyl chloride (41a) was cooled and treated with water (25.0 ml). The toluene layer was separated from the two phase aqueous mixture and the aqueous layer was extracted with methylene chloride (20.0 ml) and the organic extract was combined with the toluene mother liquor and evaporated to afford a red oil. This was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the solution was heated under reflux for 18 h. The resulting solution was evaporated to give a red oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) then with water (2 x 10.0 ml) and evaporated to give a red oil which was flash-chromatographed over silica.

Elution with toluene yielded unreacted 2-chloro-6-nitrotoluene (33) as an oil (41%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with toluene through methylene chloride and ethyl acetate to methanol gave only a series of intractable gums and oils from which no identifiable material could be obtained.

(vii) The mixture from the condensation of 2-nitrotoluene (27f) with dimethylformamide dimethyl acetal then reaction with 4-chlorobenzoyl chloride (41c) was cooled, treated with water (25.0 ml) and filtered to afford 4-chlorobenzoic anhydride (44) (30%) m.p. 195° identical (m.p. and i.r. spectrum) to an authentic sample.

The toluene layer was separated from the two phase filtrate and evaporated to give a brown oil. This was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture was heated under reflux for 18 h. The resulting solution was evaporated to afford a brown oily solid which was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated, to afford a red-brown oil which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) gave unreacted 2-nitrotoluene (27f) as an oil (28%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with hexane-methylene chloride through ethyl acetate to ethanol gave only a series of intractable oils and gums which were not further investigated.

(viii) The mixture from the condensation of 2-nitrotoluene (27f) with dimethylformamide dimethyl acetal then reaction with 4-nitrobenzoyl chloride (41d) was cooled and treated with water (25.0 ml). The twophase mixture obtained was decanted from some brown gum and the toluene layer was separated and evaporated to afford a brown oil. This was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture heated under reflux for 18 h. The resulting solution was evaporated to give a red oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to afford a brown oil which was flash-chromatographed over silica.

Elution with toluene gave unreacted 2-nitrotoluene (27f) as an oil (28%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with toluene afforded red oils followed by 2-(2-nitrophenyl)-1-(4-nitrophenyl)ethanone (24d) (7%)

[10% based on unrecovered 2-nitrotoluene (27f)] which formed colourless crystals m.p. 133° (from light petroleum-toluene), ν_{\max} 1690 (CO) and 1530 and 1350 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.36 (2H, d, J 9Hz, ArH), 8.41-8.09 (4H, m, ArH), 8.17 (2H, d J 9Hz, ArH) and 4.73 (2H, s, CH_2).

Found: C, 58.8; H, 3.4; N, 9.9%; M^+ , 286.

$\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_5$ requires: C, 58.7; H, 3.5; N, 9.8%; M, 286.

Elution with methylene chloride through ethyl acetate to methanol gave only intractable oils from which no identifiable material could be obtained.

- (c) By reaction of 2-nitrotoluene derivatives (27) with dimethylformamide diethyl acetal and in situ triethylamine-catalysed condensation of the resulting 1-(N,N-dimethylamino)-2-(2-nitroaryl)ethenes (38) with aroyl chlorides (41) followed by hydrolysis

A solution of the corresponding 2-nitrotoluene derivative (27) (0.025 mol) in anhydrous dimethylformamide (10.0 ml) was stirred and treated dropwise at room temperature with dimethylformamide diethyl acetal (0.028 mol) and the mixture was stirred and heated under reflux with the exclusion of atmospheric moisture for 26 h. The dimethylformamide was removed from the resulting red solution by distillation under reduced pressure at 70°/0.5 mmHg to afford the corresponding

1-(N,N-dimethylamino)-2-(2-nitroaryl)ethene (38) as a viscous red oil. This was dissolved in anhydrous toluene (25.0 ml) and the solution was stirred and treated dropwise at room temperature with triethylamine (2.5 g; 0.025 mol) then with the corresponding aroyl chloride (41) (0.025 mol). The mixture was stirred and heated under reflux with the exclusion of atmospheric moisture for 15 h., then worked up as described for the individual reactions below.

(i) The mixture from the condensation of 2-nitrotoluene (27f) with dimethylformamide diethyl acetal then reaction with benzoyl chloride (41a) was cooled, treated with water (25.0 ml) and the organic layer was separated and evaporated to afford a red oil which was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the solution heated under reflux for 18 h. The resulting brown solution was evaporated to yield a brown oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to give a brown oil which was flash-chromatographed over silica.

Elution with toluene-methylene chloride (1:1) yielded unreacted 2-nitrotoluene (27f) as an oil (11%) identical (i.r. spectrum) to an authentic sample.

Elution with toluene-methylene chloride (1:1) followed by methylene chloride afforded 2-(2-nitrophenyl)-1-phenyl-

ethanone (32f) (38%) [42% based on unrecovered 2-nitrotoluene (27f)] m.p. 77° (lit.⁴⁸, 81°) identical (i.r. spectrum) to an authentic sample.

Further elution with methylene chloride followed by methanol gave oils whose t.l.c. in methylene chloride over silica showed them to be close-running multi-component mixtures from which no identifiable material could be obtained.

(ii) The mixture from the condensation of 4-chloro-2-nitrotoluene (27d) with dimethylformamide diethyl acetal then reaction with benzoyl chloride (41a) was cooled and treated with water (25.0 ml). The toluene layer was separated and evaporated to give a red oil which was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the solution was heated under reflux for 18 h. The resulting brown solution was evaporated to afford a brown gummy solid which was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to yield a brown gummy solid which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) gave unreacted 4-chloro-2-nitrotoluene (27d) as an oily solid (11%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with hexane-methylene chloride (1:1) afforded 2-(4-chloro-2-nitrotoluene)-1-phenylethanone (32d) (50%) [56% based on unrecovered 4-chloro-2-nitrotoluene (27d)] m.p. 118° identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with methylene chloride followed by ethyl acetate then ethanol gave oils whose t.l.c. in methylene chloride over silica showed them to be unresolvable multi-component mixtures which were not further investigated.

(iii) The mixture from the condensation of 2,4-dinitrotoluene (27e) with dimethylformamide diethyl acetal then reaction with benzoyl chloride (41a) was cooled, treated with water (25.0 ml) and filtered to remove some dark intractable solid. The toluene-water mother liquor was separated and the toluene layer evaporated to give a red oil which was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture heated under reflux for 18 h. The resulting brown solution was evaporated to afford a brown oil which was dissolved in methylene chloride (25.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to yield a brown oil. This was flash-chromatographed over silica.

Elution with light petroleum-methylene chloride (1:1) gave unreacted 2,4-dinitrotoluene (27e) as an oily solid (7%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with light petroleum-methylene chloride (2:1) yielded the known^{54,55} 2-(2,4-dinitrophenyl)-1-phenyl-ethanone (32e) (1%) which formed brown crystals m.p. 136° (lit.,^{54,55} 136°) (from light petroleum-toluene) ν_{\max} 1680 (CO) and 1525 and 1345 (NO₂) cm⁻¹, δ_{H} (CDCl₃) 9.05 (1H, d J 2Hz, ArH), 8.46 (1H, dd J_{ortho} 8Hz J_{meta} 2Hz, ArH), 8.09-7.97 (2H, m, ArH), 7.68-7.50 (4H, m, ArH) and 5.29 (2H, s, CH₂).

Found: C, 58.7; H, 3.5; N, 9.8%; M⁺, 286.

Calc. for C₁₄H₁₀N₂O₅: C, 58.7; H, 3.5; N, 9.8%; M, 286.

Further elution with methylene chloride through ethyl acetate to methanol yielded only gums whose t.l.c. in methylene chloride over silica showed them to be complex mixtures which were not further investigated.

(iv) The mixture from the condensation of 2-nitro-toluene (27f) with dimethylformamide diethyl acetal then reaction with 4-methylbenzoyl chloride (41b) was cooled and treated with water (25.0 ml). The toluene layer was separated from the resulting two phase mixture and evaporated to afford a brown oil which was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture heated under reflux for 18 h. The resulting brown solution was evaporated and the oil obtained was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to yield a brown oil which was flash-chromatographed over silica.

Elution with toluene gave unreacted 2-nitrotoluene (27f) as an oil (17%) identical (i.r. spectrum) to an authentic sample.

Elution with hexane-methylene chloride (1:1) through methylene chloride and ethyl acetate to ethanol gave only a series of gums and oils whose t.l.c. in methylene chloride-toluene over silica showed them to be close-running multi-component mixtures which were not further investigated.

(v) The mixture from the condensation of 2-nitrotoluene (27f) with dimethylformamide diethyl acetal then reaction with 4-methoxybenzoyl chloride (4e) was cooled and treated with water (25.0 ml). The precipitated solid was collected washed with 10% w/v aqueous sodium hydrogen carbonate solution (50.0 ml) and water (25.0 ml) to afford 2-dimethylamino-1-(4-methoxybenzoyl)-1-(2-nitrophenyl)ethene (42e) (49%) which formed light brown crystals, m.p. 164° (from toluene) ν_{\max} 1625 (CO) and 1515 and 1355 (NO₂) cm⁻¹, δ_{H} (CDCl₃) 7.92 (1H, dd J_{ortho} 7.5Hz J_{meta} 2Hz, ArH), 7.54-7.24 (4H, m, ArH and CH), 7.52 (2H, d J 9Hz, ArH), 6.85 (2H, d J 9Hz, ArH), 3.83 (3H, s, CH₃O) and 2.74 (6H, s, 2 x CH₃)

Found: C, 66.2; H, 5.6; N, 8.5%; M^+ , 326.

C₁₈H₁₈N₂O₄ requires: C, 66.3; H, 5.6; N, 8.6%; M, 326.

The two phase toluene-water mother liquor was separated and the organic layer was evaporated to give a brown oil which was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml)

and the mixture heated under reflux for 18 h. The resulting brown solution was evaporated to yield a brown gummy solid. This was treated with methylene chloride (25.0 ml) and the insoluble solid collected and combined with a second crop obtained by washing the methylene chloride extract with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) followed by acidifying the combined aqueous extracts with aqueous 2M hydrochloric acid, to afford 4-methoxybenzoic acid (13%), m.p. 182° identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the methylene chloride extract gave a brown oil which was flash-chromatographed over silica.

Elution with methylene chloride-hexane (1:1) afforded unreacted 2-nitrotoluene (27f) as an oil (8%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with methylene chloride hexane (2:1), through methylene chloride and ethyl acetate to methanol gave only a series of oils and gums whose t.l.c. in methylene chloride over silica showed them to be complex mixtures which were not therefore further investigated.

(vi) The mixture from the condensation of 2-nitrotoluene (27f) with dimethylformade diethylacetal then reaction with 4-chlorobenzoyl chloride (41c) was cooled and treated with water (25.0 ml) and filtered to give an orange-brown solid. This was washed with 10% w/v aqueous sodium hydrogen

carbonate solution (50.0 ml) and water (25.0 ml) and dried in vacuo then flash-chromatographed over silica.

Elution with methylene chloride afforded 4-chloro-benzoic anhydride (44) (15%) which formed colourless plates m.p. 196° (from light petroleum-toluene), ν_{\max} 1785 and 1720 (CO) cm^{-1} , δ_{H} (CDCl_3) 8.06 (2H, d J 9 Hz, ArH) and 7.50 (2H, d J 9Hz, ArH).

Found: C, 56.8; H, 2.7%; M^+ , 298, 296, 294.

Calc. for $\text{C}_{14}\text{H}_8\text{Cl}_2\text{O}_3$: C, 56.9; H, 2.7%; M, 295.

Elution with methanol gave 1-(4-chlorobenzoyl)-2-dimethylamino-1-(2-nitrophenyl)ethene (42c) (31%) which formed orange crystals m.p. 159° (from toluene), ν_{\max} 1630 (CO) and 1510 and 1345 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 7.93 (1H, dd J_{ortho} 8Hz J_{meta} 2Hz, ArH), 7.69-7.26 (7H, m, ArH), 7.20 (1H, s, CH) and 2.74 (6H, s, 2 x CH_3).

Found: C, 62.1; H, 4.6; N, 8.2%; M^+ , 332, 330.

$\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_3$: C, 61.7; H, 4.5; N, 8.5%; M, 330.5.

The original two-phase toluene-water mother liquor was separated and the organic layer was evaporated to yield a brown oil which was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture heated under reflux for 18 h. The resulting brown solution was evaporated and the residual oil was dissolved in methylene chloride (25.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen

carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to obtain a brown oil which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) afforded unreacted 2-nitrotoluene (27f) as an oil (17%) identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with hexane-methylene chloride (1:1) gave 1-(4-chlorophenyl)-2-(2-nitrophenyl)ethanone (24c) (20%) [24% based on unrecovered 2-nitrotoluene (27f)] which formed colourless crystals m.p. 84° (from light petroleum-toluene), ν_{\max} 1685 (CO) and 1515 and 1340 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.16 (1H, dd J_{ortho} 7.5Hz J_{meta} 1.5Hz, ArH), 7.97 (2H, d J 9Hz, ArH), 7.64-7.28 (3H, m, ArH), 7.47 (2H, d J 9 Hz, ArH), and 4.68 (2H, s, CH_2).

Found: C, 60.9; H, 3.5; N, 4.9%; M^+ , 277 and 275.

$\text{C}_{14}\text{H}_{10}\text{ClNO}_3$ requires: C, 61.0; H, 3.6; N, 5.1%; M, 275.5.

Elution with methylene chloride and methanol gave a brown oil whose t.l.c. in methylene chloride-light petroleum over silica showed it to be a close-running multicomponent mixture which was not further investigated.

(vii) The mixture from the condensation of 2-nitrotoluene (27f) with dimethylformamide diethylacetal then reaction with 4-nitrobenzoyl chloride (4ld) was cooled and treated with water (25.0 ml) and the solid obtained collected, washed with 10% w/v aqueous sodium hydrogen carbonate solution

(50.0 ml) and water (25.0 ml) to afford 2-dimethylamino-1-(4-nitrobenzoyl)-1-(2-nitrophenyl)ethene (42d) (57%) which formed red-brown crystals, m.p. 183° (from toluene) ν_{\max} 1605 (CO) and 1515 and 1355 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.15 (2H, d J 9Hz, ArH), 7.94 (1H, dd J_{ortho} 7.5 Hz J_{meta} 1.5 Hz, ArH), 7.57 (2H, d J 9Hz, ArH), 7.50-7.19 (3H, m, ArH), 7.12 (1H, s, ArH) and 2.73 (6H, s, 2 x CH_3).

Found: C, 59.7; H, 4.4; N, 12.1%; M^+ , 341.

$\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_5$ requires: C, 59.8; H, 4.4; N, 12.3%; M, 341.

The original toluene-water mother liquor was separated and the toluene layer was evaporated to give a brown oil which was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture heated under reflux for 18 h. The mixture was cooled and evaporated to give a brown oil. This was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to afford a brown oil which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) gave unreacted 2-nitrotoluene (27f) as an oil (7%) identical (i.r. spectrum) to an authentic sample.

Further elution with hexane-methylene chloride (1:1) through methylene chloride and ethyl acetate to methanol gave only intractable gums from which no identifiable could be obtained.

(d) By hydrolysis of 1-aro₁yl-2-(N,N-dimethyl-amino)-1-(2-nitroaryl)ethenes (42)

A solution of the corresponding 1-aro₁yl-2-(N,N-dimethyl-amino)-1-(2-nitroaryl)ethene (42) (0.02 mol) in 1,4-dioxane (50.0 ml) and water (16.0 ml) was heated under reflux for 18 h. The resulting solution was evaporated to remove the dioxane and the resulting aqueous mixture was extracted with methylene chloride (50.0 ml) to give a solid or an oil which was purified by flash-chromatography.

(i) The hydrolysis of 1-benzoyl-2-dimethylamino-1-(5-methoxy-2-nitrophenyl)ethene (39c) gave a brown solid which was flash-chromatographed over silica.

Solution with methylene chloride yielded 2-(5-methoxy-2-nitrophenyl)-1-phenylethanone (32c) (80%) which formed colourless needles m.p. 129° (from toluene), ν_{\max} 1680 (CO) and 1580 and 1340 (NO₂) cm⁻¹, δ_{H} (CDCl₃) 8.21 (1H, d J 9Hz, ArH), 8.08-7.96 (2H, m, ArH), 7.60-7.25 (3H, m, ArH), 6.98-6.77 (2H, m, ArH), 4.69 (2H, s, CH₂) and 3.87 (3H, s, CH₃).

Found: C, 66.6; H, 4.8; N, 5.2%; M⁺, 271.

C₁₅H₁₃NO₄ requires: C, 66.4; H, 4.8; N, 5.2%; M, 271.

Further elution with ethyl acetate through to methanol gave only gums from which no identifiable material could be obtained.

(ii) The hydrolysis of 2-dimethylamino-1-(4-methoxybenzoyl)-1-(2-nitrophenyl)ethene (42e) gave a brown solid which was flash-chromatographed over silica.

Elution with methylene chloride afforded 1-(4-methoxyphenyl)-2-(2-nitrophenyl)ethanone (24e) (93%) m.p. 118° identical (m.p. and i.r. spectrum) to an authentic sample obtained before.

Further elution with methanol gave only a gum whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

(iii) The hydrolysis of 1-(4-chlorobenzoyl)-2-dimethylamino-1-(2-nitrophenyl)ethene (42d) gave a brown oil which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (2:1) yielded 1-(4-chlorophenyl)-2-(2-nitrophenyl)ethanone (24c) (72%) m.p. 73°, identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-methylene chloride (2:1) through methylene chloride to methanol gave only gums and oils whose t.l.c. in methylene chloride or ethyl acetate over silica showed them to be multicomponent mixtures which were not further investigated.

(iv) The hydrolysis of 2-dimethylamino-1-(4-nitro-benzoyl)-1-(2-nitrophenyl)ethene (42d) gave a brown solid which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (2:1) afforded 1-(4-nitrophenyl)-2-(2-nitrophenyl)ethanone (24d) (86%) m.p. 134°C identical (m.p. and i.r. spectrum) to an authentic sample obtained before.

Elution with methylene chloride through to methanol yielded only intractable gums whose t.l.c. in methylene chloride over silica showed them to be multicomponent mixtures which were not further investigated.

2-(5-Methoxy-2-nitrophenyl)-1-phenylethanone Oxime (32c);
(C=NOH for C=O)

A solution of 2-(5-methoxy-2-nitrophenyl)-1-phenylethanone (32c) (0.27 g; 0.001 mol) in ethanol (7.0 ml) was treated with a solution of hydroxyammonium chloride (0.56 g; 0.008 mol) in water (11.0 ml) followed by a solution of anhydrous sodium acetate (0.66 g; 0.008 mol) in water (3.0 ml) and the mixture was heated under reflux for 1 h. The resulting clear solution was cooled and evaporated to afford a gummy solid which was treated with water (2.0 ml) and extracted with methylene chloride (2 x 5.0 ml) to give 2-(5-methoxy-2-nitrophenyl)-1-phenylethanone oxime (32c); C=NOH for C=O (0.29 g; quant.) which formed colourless crystals, m.p. 102° (from light petroleum-toluene) ν_{\max} 1610 (C=N) and 1535 and 1340 (NO₂) cm⁻¹.

Found: C, 62.9; H, 4.9; N, 9.6%; ($M^+ + 1$), 287.

$C_{15}H_{14}N_2O_4$ requires: C, 62.9; H, 4.9; N, 9.8%; M, 286.

2-Bromo-2-(2-nitroaryl)-1-arylethanones (45)

A solution of the corresponding (2-nitroaryl)-1-arylethanone (32) (0.02 mol) in anhydrous 1,2-dimethoxyethane (50.0 ml) was treated dropwise with stirring with a solution of bromine (0.04 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) and the mixture was stirred overnight at room temperature with the exclusion of atmospheric moisture. The resulting solution was evaporated to afford a gummy solid which was dissolved in methylene chloride (25.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 40.0 ml) and water (40.0 ml) and evaporated to give a solid which was then purified as described for the individual reactions below.

(a) The bromination of 2-(2-nitrophenyl)-1-phenylethanone (24a) (4.8 g; 0.02 mol) gave the known⁶⁴ 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (58a) (5.3 g; 91%) which formed colourless crystals, m.p. 116° (from toluene) (lit.,⁶⁴ 116°).

(b) The bromination of 2-(4-methyl-2-nitrophenyl)-1-phenylethanone (32a) (5.1 g; 0.02 mol) yielded 2-bromo-2-(4-methyl-2-nitrophenyl)-1-phenylethanone (45a) (6.1 g; 92%) which formed colourless crystals m.p. 123° (from toluene),

ν_{\max} 1680 (CO) and 1525 and 1350 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.13-7.46 (8H, m, ArH), 7.12 (1H, s, CH) and 2.46 (3H, s, CH_3).

Found: C, 53.3; H, 3.5; N, 4.1%; ($\text{M}^+ - \text{HBr}$), 237.

$\text{C}_{15}\text{H}_{12}\text{BrNO}_3$ requires: C, 53.9; H, 3.6; N, 4.2%; M, 334.

Found: ($\text{M} + \text{H}$) $^+$ (FAB), 336.0060.

$\text{C}_{15}\text{H}_{12}^{81}\text{BrNO}_3$ requires: ($\text{M} + \text{H}$), 336.0060.

Found: ($\text{M} + \text{H}$) $^+$ (FAB), 334.0079.

$\text{C}_{15}\text{H}_{12}^{79}\text{BrNO}_3$ requires: ($\text{M} + \text{H}$), 334.0079.

(c) The bromination of 2-(5-methyl-2-nitrophenyl)-1-phenylethanone (32b) (5.1 g; 0.02 mol) gave 2-bromo-2-(5-methyl-2-nitrophenyl)-1-phenylethanone (52) (6.4 g; 96%) which formed colourless crystals, m.p. 110° (from diethyl ether), ν_{\max} 1680 (CO) and 1515 and 1340 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.06 (1H, d J 2Hz, ArH), 7.81-7.52 (7H, m, ArH), 7.16 (1H, brs, CH) and 2.52 (3H, s, CH_3).

Found: C, 53.8; H, 3.4; N, 4.0%; ($\text{M}^+ - \text{NO}_2$), 289, 287.

$\text{C}_{15}\text{H}_{12}\text{BrNO}_3$ requires: C, 53.9; H, 3.6; N, 4.2%; M, 334.

(d) The attempted bromination of 2-(5-methoxy-2-nitrophenyl)-1-phenylethanone (32c) (5.5 g; 0.02 mol) gave a red solid (6.8 g) which was flash-chromatographed over silica.

Elution with toluene gave a red solid (6.3 g) which decomposed on standing and could not be purified for characterisation.

(e) The bromination of 2-(4-chloro-2-nitrophenyl)-1-phenylethanone (32d) (5.5 g; 0.02 mol) gave a brown solid (5.8 g) m.p. 93-95° whose t.l.c. in methylene chloride-light petroleum (2:1) over silica showed the presence of unreacted ketone (32d). The solid was redissolved in anhydrous 1,2-dimethoxyethane (50.0 ml) and the solution was treated with a solution of bromine (3.2 g; 0.04 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) and the mixture stirred overnight at room temperature with the exclusion of atmospheric moisture. The solution was evaporated and the residue was dissolved in methylene chloride (40.0 ml) and the solution washed with 10% aqueous sodium hydrogen carbonate solution (2 x 40.0 ml) then water (2 x 20.0 ml) and evaporated to obtain 2-bromo-2-(4-chloro-2-nitrophenyl)-1-phenylethanone (45b) (6.5 g; 92%) which formed colourless crystals, m.p. 127° (from light petroleum-toluene), ν_{\max} 1685 (CO) and 1530 and 1350 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.13-7.39 (8H, m, ArH) and 7.07 (1H, s, CH).

Found: C, 47.7; H, 2.5; N, 3.9%; M^+ , 356 and 354.

$\text{C}_{14}\text{H}_9\text{BrClNO}_3$ requires: C, 47.4; H, 2.5; N, 4.0%; M, 354.5.

(f) The attempted bromination of 2-(6-chloro-2-nitrophenyl)-1-phenylethanone (37) (5.5 g; 0.02 mol) gave a gummy solid (5.4 g). This was triturated with ether to give unreacted 2-(6-chloro-2-nitrophenyl)-1-phenylethanone (37) (3.1 g; 56%) m.p. 98° identical (m.p. and i.r. spectrum) to an authentic sample prepared previously.

The ether mother liquor was evaporated to obtain an oil (2.3 g) from which no identifiable material could be obtained.

(g) The bromination of 1-(4-methylphenyl)-2-(2-nitrophenyl)ethanone (24b) (5.2 g; 0.02 mol) afforded a brown solid (6.2 g) which was crystallised from toluene to give 2-bromo-1-(4-methylphenyl)-2-(2-nitrophenyl)ethanone (58b) (5.6 g; 84%) as colourless plates, m.p. 111° ν_{\max} 1680 (CO) and 1525 and 1345 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.09-8.02 (2H, m, ArH), 7.98 (2H, d J 8Hz, ArH), 7.73 (1H, m, ArH), 7.57 (1H, m, ArH), 7.33 (2H, d J 9Hz, ArH), 7.12 (1H, s, CH) and 2.44 (3H, s, CH_3).

Found: C, 53.6; H, 3.6; N, 4.2%; M^+ , 335 and 333.

$\text{C}_{15}\text{H}_{12}\text{BrNO}_3$ requires: C, 53.9; H, 3.6; N, 4.2%; M, 334.

(h) The bromination of 1-(4-methoxyphenyl)-2-(2-nitrophenyl)ethanone (24e) (5.4 g; 0.02 mol) afforded a red oil (7.4 g) whose t.l.c. in methylene chloride over silica showed it to contain unreacted ketone (24e). The oil was

redissolved in anhydrous 1,2-dimethoxyethane (50.0 ml) and the solution was treated with a solution of bromine (3.2 g; 0.04 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) and the mixture stirred overnight at room temperature with the exclusion of atmospheric moisture. The mixture was evaporated to give a dark oil which was dissolved in methylene chloride (50.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 40.0 ml) and evaporated to yield a red oil (8.2 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) through methylene chloride to methanol gave only a series of oils and gums from which no identifiable material could be obtained.

(i) The bromination of 1-(4-chlorophenyl)-2-(2-nitrophenyl)ethanone (24c) (5.6 g; 0.02 mol) yielded a brown solid (7.4 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) gave 2-bromo-1-(4-chlorophenyl)-2-(2-nitrophenyl)ethanone (58c) (6.4 g; 90%) which formed colourless needles, m.p. 97° (from light petroleum-toluene) ν_{\max} 1690 (CO) and 1515 and 1350 (NO₂) cm⁻¹, δ_{H} (CDCl₃) 8.13-7.57 (4H, m, ArH), 8.03 (2H, d J 9 Hz, ArH), 7.49 (2H, d J 9 Hz, ArH), and 7.07 (1H, s, CH).

Found: C, 47.2; H, 2.5; N, 4.2%; (M^+ - HOBr), 259, 257.

$C_{14}H_9BrClNO_3$ requires: C, 47.4; H, 2.5; N, 4.0%; M, 354.5.

(j) The bromination of 2-(2-nitrophenyl)-1-(4-nitrophenyl)ethanone (24d) (5.8 g; 0.02 mol) yielded a brown solid (6.0 g) whose t.l.c. in methylene chloride over silica showed it to contain unreacted ketone (24d). The solid was redissolved in anhydrous 1,2-dimethoxyethane (60.0 ml) and the solution was treated with a solution of bromine (3.2 g; 0.02 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 48 h. The mixture was evaporated to give a clear brown oil which was dissolved in methylene chloride (50.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 40.0 ml) then water (2 x 20.0 ml) and evaporated to obtain a brown oil (8.0 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) gave 2-bromo-2-(2-nitrophenyl)-1-(4-nitrophenyl)ethanone (58d) (6.8 g; 92%) which formed colourless crystals, m.p. 90° (from light petroleum-toluene) ν_{\max} 1690 (CO) and 1520 and 1345 (NO_2) cm^{-1} , δ_H ($CDCl_3$) 8.33 (2H, s, ArH), 8.29 (2H, s, ArH), 8.25-8.05 (2H, m, ArH), 7.90-7.48 (2H, m, ArH) and 7.09 (1H, s, CH).

Found: C, 46.3; H, 2.5; N, 7.7%; M^+ , 366, 364.

$C_{14}H_9BrN_2O_5$ requires: C, 46.0; H, 2.5; N, 7.7%; M, 365.

Cyclisation Reactions of 2-Bromo-2-(2-nitroaryl)-1-aryl-ethanones (45) to 3H-Indol-3-one 1-N-oxides (Isatogens) (50,51) in Glacial Acetic Acid

(a) In the absence of hydroquinone

A solution of the corresponding 2-bromo-2-(nitroaryl)-1-arylethanone (45) (0.002 ml) in glacial acetic acid (5.0 ml) was heated under reflux for 3 h. The resulting red mixture was evaporated and the residue was co-evaporated with toluene to obtain a gummy orange-red solid, which was purified as described for the individual reactions below. Ultraviolet spectra of isatogens are collected in Table (see page 75).

(i) The gummy red solid from 2-bromo-2-(4-methyl-2-nitrophenyl)-1-phenylethanone (45a) was flash-chromatographed over silica.

Elution with toluene gave 5-bromo-6-methyl-2-phenyl-isatogen (50a) (55%) which formed red crystals, m.p. 218° (from toluene) ν_{\max} 1700 (CO) cm^{-1} , δ_{H} (CDCl_3) 8.68-8.56 (2H, m, ArH), 7.77 (1H, s, H-7), 7.57 (1H, s, H-4), 7.53-7.44 (3H, m, ArH) and 2.55 (3H, s, CH_3).

Found: C, 57.1; H, 3.1; N, 4.5%; M^+ , 317 and 315.

$\text{C}_{15}\text{H}_{10}\text{BrNO}_2$ requires: C, 57.0; H, 3.2; N, 4.4%; M, 316.

Further elution with toluene gave 6-methyl-2-phenyl-isatogen (51a) (15%), identified by comparison (m.p., t.l.c. and i.r. spectrum) with an authentic sample prepared later.

Further elution with toluene through methylene chloride and ethyl acetate to methanol yielded only multicomponent mixtures from which no identifiable material could be obtained.

(ii) The gummy orange-red solid from 2-bromo-2-(5-methyl-2-nitrophenyl)-1-phenylethanone (52) was flash-chromatographed over silica.

Elution with toluene gave unreacted 2-bromo-2-(5-methyl-2-nitrophenyl)-1-phenylethanone (52) (52%) m.p. 86° identical (t.l.c. and i.r. spectrum) to an authentic sample prepared before.

Further elution with toluene yielded 5-methyl-2-phenylisatogen (57) (33%) identified by comparison (m.p., t.l.c. and i.r. spectrum) with an authentic sample, prepared later.

Further elution with toluene-methylene chloride through ethyl acetate to methanol gave only intractable gums from which no identifiable material could be obtained.

(iii) The gummy red solid from 2-bromo-2-(4-chloro-2-nitrophenyl)-1-phenylethanone (45b) was flash-chromatographed over silica.

Elution with hexane-methylene chloride gave unreacted 2-bromo-2-(4-chloro-2-nitrophenyl)-1-phenylethanone (45b) (33%) m.p. 115° identical (t.l.c. and i.r. spectrum) to an authentic sample prepared before.

Elution with hexane-methylene chloride (1:1) followed by methylene chloride yielded an orange and a red solid whose t.l.c. in light petroleum-methylene chloride over

silica showed them to be an identical two component mixture. This was subjected to medium pressure liquid chromatography over silica.

Elution with hexane-methylene chloride (1:1) gave 5-bromo-6-chloro-2-phenylisatogen (50b) (11%) [16% based on unrecovered 2-bromo-2-(4-chloro-2-nitrophenyl)-1-phenylethanone (45b)] which formed red plates, m.p. 237° (from dimethylformamide) ν_{\max} 1715 (CO) cm^{-1} , δ_{H} [(CD₃)₂SO] 8.56-8.44, (2H, m, ArH), 8.10 (1H, s, H-7), 7.97 (1H, s, H-4), 7.65-7.53 (3H, m, ArH).

Found: C, 65.4; H, 3.0; N, 5.6%; M^+ , 337 and 335.

C₁₄H₇BrClNO₂ requires: C, 65.2; H, 3.1; N, 5.4%; M, 336.5.

Further elution with hexane-methylene chloride (1:1) afforded 6-chloro-2-phenylisatogen (51b) (24%) [37% based on unrecovered 2-bromo-2-(4-chloro-2-nitrophenyl)-1-phenylethanone (45b)] which formed orange crystals, m.p. 166° (from light petroleum-toluene) ν_{\max} 1720 (CO) cm^{-1} , δ_{H} (CDCl₃) 8.69-8.53 (2H, m, ArH), 7.70-7.63 (1H, s, ArH) and 7.54-7.40 (5H, m, ArH).

Found: C, 65.4; H, 3.0; N, 5.6%; M^+ , 259 and 257.

C₁₄H₈ClNO₂ requires: C, 65.2; H, 3.1; N, 5.4%; M, 257.5.

Elution with ethyl acetate and ethanol gave brown gummy solids whose t.l.c. in ethyl acetate-methylene chloride over silica showed them to be multicomponent mixtures which were not further investigated.

(iv) The red-brown gum from 2-bromo-1-(4-methylphenyl)-2-(2-nitrophenyl)ethanone (58b) was flash-chromatographed over silica.

Elution with toluene-methylene chloride (1:1) yielded 5-bromo-2-(4-methylphenyl)isatogen (62b) (38%) which formed orange crystals, m.p. 179° (from ethyl acetate) ν_{\max} 1720 br (CO) cm^{-1} , δ_{H} (CDCl_3) 8.55 (2H, d J 8Hz, ArH), 7.87-7.71 (2H, m, ArH), 7.54 (2H, d J 8Hz, ArH), 7.36 (1H, m, ArH) and 2.41 (3H, s, CH_3).

Found: M^+ , 316.9867.

$\text{C}_{15}\text{H}_{10}^{81}\text{BrNO}_2$ requires: M, 316.9876.

Found: M^+ , 314.9884.

$\text{C}_{15}\text{H}_{10}^{79}\text{BrNO}_2$ requires: M, 314.9895.

Elution with methylene chloride afforded an orange solid which was crystallised from light petroleum-toluene to give 2-(4-methylphenyl)isatogen (63b) (26%) which formed orange crystals, m.p. 205° (from light-petroleum-toluene) ν_{\max} 1700 (CO) cm^{-1} , δ_{H} (CDCl_3) 8.63 (1H, s, ArH), 8.52 (1H, s, ArH), 7.72-7.51 (5H, m, ArH), 7.35 (1H, brs, ArH) and 2.41 (3H, s, CH_3).

Found: C, 75.9; H, 4.5; N, 6.0%; M^+ , 237.

$\text{C}_{15}\text{H}_{11}\text{NO}_2$ requires: C, 76.0; H, 4.6; N, 5.9%; M, 237.

Elution with methylene chloride-ethyl acetate (2:1) through ethyl acetate to ethanol yielded no further identifiable material.

(v) The red solid from 2-bromo-1-(4-chlorophenyl)-2-(2-nitrophenyl)ethanone (58c) was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) gave 5-bromo-2-(4-chlorophenyl)isatogen (62c) (50%) which formed red crystals, m.p. 244° (from light petroleum-toluene)

ν_{\max} 1710 (CO) cm^{-1} , δ_{H} (CDCl_3) 8.63 (2H, d J 9Hz, ArH), 7.89-7.59 (3H, m, ArH) and 7.46 (2H, d J 9Hz, ArH).

Found: C, 49.7; H, 2.1; N, 4.2%; M^+ , 337 and 335.

$\text{C}_{14}\text{H}_7\text{BrClNO}_2$ requires: C, 49.9; H, 2.1; N, 4.2%; M, 336.5

Further elution with hexane-methylene chloride (1:1) yielded an orange solid which was purified by medium pressure liquid chromatography over silica.

Elution with methylene chloride afforded the known^{25,18} 2-(4-chlorophenyl)isatogen (63c) (20%) which formed orange crystals, m.p. 177° (from light petroleum-toluene) (lit.^{25,18}, 175°), ν_{\max} 1710 (CO) cm^{-1} , δ_{H} (CDCl_3) 8.65 (2H, d J 8 Hz, ArH), 7.75-7.55 (4H, m, ArH) and 7.45 (2H, d J 8Hz, ArH).

Found: C, 64.2; H, 3.0; N, 5.4%; M^+ , 259 and 257.

Calc. for $\text{C}_{14}\text{H}_8\text{ClNO}_2$: C, 65.2; H, 3.1; N, 5.4%; M, 257.5

Found: M^+ , 259.0203

Calc. for $\text{C}_{14}\text{H}_8^{37}\text{ClNO}_2$: M, 259.0214

Found: M^+ , 257.0238

Calc. for $\text{C}_{14}\text{H}_8^{35}\text{ClNO}_2$: M, 257.0244

Elution with methylene chloride then methanol yielded no further identifiable material.

(vi) The gummy orange solid from 2-bromo-2-(2-nitrophenyl)-1-(4-nitrophenyl)ethanone (58d) was flash-chromatographed over silica.

Elution with methylene chloride-hexane (2:1) and methylene chloride yielded a series of orange solids (total 0.71 g) whose t.l.c. in methylene chloride over silica showed them to be identical two component mixtures. These were combined and subjected to medium pressure liquid chromatography over silica.

Elution with hexane-methylene chloride (1:1) afforded 5-bromo-2-(4-nitrophenyl)isatogen (62d) (45%) which formed red-purple crystals, m.p. 269° (from dimethylformamide) ν_{\max} 1710 (CO) and 1515 and 1350 (NO_2) cm^{-1} .

Found: C, 48.3; H, 2.1; N, 8.0%; M^+ , 348 and 346.

$\text{C}_{14}\text{H}_7\text{BrN}_2\text{O}_4$ requires: C, 48.4; H, 2.0; N, 8.1%; M, 347.

Further elution with hexane-methylene chloride (1:1) gave the known^{15,13} 2-(4-nitrophenyl)isatogen (63d) (30%) which formed orange crystals, m.p. 260° (from ethyl acetate-dimethylformamide) (lit.^{15,13}, 254°), ν_{\max} 1710 (CO) and 1510 and 1350 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.75 (2H, d J 8Hz, ArH) 8.40 (2H, d J 8Hz, ArH) and 7.84-7.74 (4H, brm, ArH).

Found: C, 61.5; H, 3.0; N, 10.2%; M^+ , 268.

Calc. for $C_{14}H_8N_2O_4$: C, 62.7; H, 3.0; N, 10.5%; M, 268.

Found: M^+ , 268.0478

Calc. for $C_{14}H_8N_2O_4$: M, 268.0484

Elution with methylene chloride-ethyl acetate (4:1) through ethyl acetate to methanol yielded no further identifiable material.

(b) In the presence of hydroquinone

A solution of the corresponding 2-bromo-2-(nitroaryl)-1-arylethanone (45) (0.002 mol) in glacial acetic acid (5.0 ml) was treated with hydroquinone (0.22 g; 0.002 mol) and the mixture was heated under reflux for 3 h. The resulting red solution was evaporated to afford a red oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with 2M aqueous sodium hydroxide (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to yield a gummy orange-red solid which was purified as described for the individual reactions below. Ultraviolet spectra of isatogens are collected in Table (see page 75).

(i) The gummy orange-red solid from 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (58a) was flash-chromatographed in toluene over silica to give 2-phenylisatogen (63a) (36%) which formed red crystals m.p. 185° (lit.^{15,13}, 186°) (from ethyl acetate) ν_{\max} 1705 (CO) and 1520 and 1335 (NO_2) cm^{-1} , δ_H ($CDCl_3$) 8.72-8.59 (2H, m, ArH) and 7.75-7.44 (7H, m, ArH).

Found: C, 74.3; H, 3.8; N, 6.1%; M^+ , 223.

Calc. for $C_{14}H_9NO_2$: C, 75.3; H, 3.6; N, 6.3%; M, 223.

Found: M^+ , 223.0641

Calc. for $C_{14}H_9NO_2$: M, 223.0633.

(ii) The gummy orange-red solid from 2-bromo-2-(4-methyl-2-nitrophenyl)-1-phenylethanone (45a) was flash-chromatographed over silica.

Elution with toluene gave 5-bromo-6-methyl-2-phenylisatogen (50a) (11%) m.p. 218° identical (m.p., t.l.c. and i.r. spectrum) to an authentic sample obtained before.

Further elution with toluene gave 6-methyl-2-phenylisatogen (51a) (73%) which formed red plates m.p. 191° (from toluene) ν_{\max} 1710 (CO) cm^{-1} , δ_H (CDCl_3) 8.70-8.58 (2H, m, ArH), 7.57-7.25 (6H, m, ArH) and 2.51 (3H, s, CH_3).

Found: C, 75.7; H, 4.6; N, 5.9%; M^+ , 237.

$C_{15}H_{11}NO_2$ requires: C, 76.0; H, 4.6; N, 5.9%; M, 237.

Elution with methylene chloride through ethyl acetate to methanol yielded no further identifiable material.

(iii) The red gum from 2-bromo-2-(5-methyl-2-nitrophenyl)-1-phenylethanone (52) was flash-chromatographed over silica.

Elution with toluene yielded 5-methyl-2-phenylisatogen (57) (64%) which formed red plates m.p. 185° (from toluene) ν_{\max} 1710 br (CO) cm^{-1} , δ_{H} (CDCl_3) 8.69-8.56 (2H, m, ArH), 7.63-7.39 (6H, m, ArH) and 2.48 (3H, s, CH_3).
Found: C, 75.9; H, 4.6; N, 6.0%; M^+ , 237.
 $\text{C}_{15}\text{H}_{11}\text{NO}_2$ requires: C, 76.0; H, 4.6; N, 5.9%; M, 237.

Further elution with methylene chloride through ethyl acetate to methanol afforded no other identifiable material.

2-Chloro-2-(2-nitrophenyl)-1-phenylethanone (64)

(a) A solution of 2-(2-nitrophenyl)-1-phenylethanone (24a) (0.24 g; 0.001 mol) in anhydrous toluene (5.0 ml) was stirred and heated to 40° (water bath) and treated dropwise with the exclusion of atmospheric moisture with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous toluene (2.5 ml) and the mixture was stirred and heated at 40° for 1 h. The resulting solution was cooled and treated with further sulphuryl chloride (0.27 g; 0.002 mol) and stirring and heating at 40° with exclusion of atmospheric moisture continued for 48 h. The mixture was cooled and evaporated to afford a brown oil (0.56 g) which was flash-chromatographed over silica.

Elution with toluene gave 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64) (0.13 g; 46%) which formed colourless crystals m.p. 108° (from light petroleum-toluene) ν_{\max} 1690 (CO)

and 1525 and 1345 (NO_2) cm^{-1} , δ_{H} (CDCl_3) 8.25-7.95 (4H, m, ArH), 7.90-7.40 (5H, m, ArH) and 7.10 (1H, s, CH).

Found: C, 61.2; H, 3.5; N, 4.9%; M^+ , 277, 275.

$\text{C}_{14}\text{H}_{10}\text{ClNO}_3$ required: C, 61.0; H, 3.6; N, 5.1%; M, 275.5.

Elution with toluene-methylene chloride then ethyl acetate afforded an oil which solidified on standing and was crystallised from ether to give unreacted 2-(2-nitrophenyl)-1-phenylethanone (24a) (0.13 g; 54%) m.p. 78° (lit.⁴⁸ 81°) identical (i.r. spectrum) to an authentic sample.

(b) A solution of 2-(2-nitrophenyl)-1-phenylethanone (24a) (2.4 g; 0.01 mol) in anhydrous toluene (25.0 ml) was stirred and heated to 40° (oil bath) then treated with sulphuryl chloride (5.4 g; 0.04 mol) followed by pyridine (0.85 g; 0.01 mol) and the mixture was heated at 40° for 2.5 h. with the exclusion of atmospheric moisture. The mixture was evaporated to give an oil which was dissolved in methylene chloride (30.0 ml) and the solution washed with 2M aqueous hydrochloric acid (25.0 ml) and evaporated to afford a light brown oil solid (3.5 g) which was flash-chromatographed in hexane-methylene chloride (1:1) over silica to afford 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64) (2.2 g; 80%) which formed colourless plates m.p. 108° (from light petroleum-toluene), identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

The Attempted Cyclisation of 2-Chloro-2-(2-nitrophenyl)-1-phenylethanone (64) in Glacial Acetic Acid

A solution of 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64) (0.55 g; 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 27 h. and the resulting red solution was evaporated to give a red-brown gummy solid (0.51 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) afforded an oil (0.14 g) from which no identifiable material could be obtained.

Elution with hexane-methylene chloride yielded benzoic acid (0.11 g) m.p. 115° which liberated carbon dioxide from aqueous 10% w/v sodium hydrogen carbonate solution and was identical (i.r. spectrum) to an authentic sample.

Further elution with hexane-methylene chloride (1:1) gave 1-benzoyl-2,1-benzisoxazole (77) (0.10 g; 21%) which formed colourless needles m.p. 154° (from toluene-light petroleum) (lit.⁶⁹ , 154°) ν_{\max} 1780 (CO) and 1695-1675 br (CO) cm^{-1} , δ_{H} (CDCl_3) 8.35-8.20 (1H, m, ArH) and 8.10-7.30 (8H, m, ArH).

Found: C, 70.0; H, 3.8; N, 5.9%; M^+ , 239.

Calc. for $\text{C}_{14}\text{H}_9\text{NO}_3$: C, 70.2; H, 3.7; N, 5.9%; M, 239.

5-Chloro-2-phenylisatogen (67)

A solution of 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64) (1.1 g; 0.004 mol) in glacial acetic acid (10.0 ml) was stirred and treated with a steady flow of anhydrous hydrogen chloride at room temperature for 10 min. with the exclusion of atmospheric moisture. The resulting solution was then heated under reflux for 3 h. with continual passage of hydrogen chloride. The clear solution was evaporated to afford a red oil (1.3 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) afforded unreacted 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64) (0.85 g; 77%) m.p. 81° identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with hexane-methylene chloride (2:1) yielded 5-chloro-2-phenylisatogen (67) (0.17 g; 22%) [74% based on unrecovered 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64)] which formed orange plates m.p. 186° (from toluene) ν_{\max} 1715 (CO) cm^{-1} , δ_{H} (CDCl_3) 8.67-8.55 (2H, m, ArH) and 7.64-7.44 (6H, m, ArH).

Found: C, 64.7; H, 3.1; N, 5.4%; M^+ , 259 and 257

$\text{C}_{14}\text{H}_8\text{ClNO}_2$ requires: C, 65.2; H, 3.1; N, 5.4%; M, 257.5.

Found: M^+ , 257.0221

$\text{C}_{14}\text{H}_8^{35}\text{ClNO}_2$ requires: M, 257.0244

Found: M^+ , 259.0191

$\text{C}_{14}\text{H}_8^{37}\text{ClNO}_2$ requires: M, 259.0214

Further elution with methylene chloride through ethyl acetate to methanol gave no other identifiable material.

2-Phenylisatogen (63a)

A solution of 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64) (0.55 g; 0.002 mol) in glacial acetic acid (5.0 ml) was treated with hydroquinone (0.22 g; 0.002 mol) and the mixture was heated under reflux for 3h. The resulting red solution was then evaporated to afford a red oil (0.79 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) yielded unreacted 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64) (0.27 g; 49%) m.p. 75° identical (t.l.c. and i.r. spectrum) to an authentic sample.

Further elution with hexane-methylene chloride (2:1) gave a gummy red solid (0.19 g) which was triturated with diethyl ether to yield 2-phenylisatogen (63a) (0.09 g; 20%) [40% based on unrecovered 2-chloro-2-(2-nitrophenyl)-1-phenylethanone (64)], m.p. 185° (lit.^{15,13}, 186°) identical (mixed m.p., t.l.c., and i.r. spectrum) to an authentic sample prepared before.

Final elution with ethyl acetate-ethanol gave a purple gum (0.22 g) from which no identifiable material could be obtained.

2-Methyl-4-(2-nitrobenzylidene)oxazolin-5-one (78)

2-Methyl-4-(2-nitrobenzylidene)oxazolin-5-one (78) was prepared by the reaction of 2-nitrobenzaldehyde with N-acetylglycine in acetic anhydride in the presence of sodium acetate as described by Johnson et al.⁷¹, (yield 60%), m.p. 107° (lit.⁷¹, 112°).

3-(2-Nitrophenyl)-2-oxopropanoic Acid (80)

3-(2-Nitrophenyl)-2-oxopropanoic acid (80) was prepared by the reaction of 2-methyl-4-(2-nitrobenzylidene)-oxazolin-5-one (78) with hydrochloric acid as described by Johnson et al.⁷¹, (yield 89%), m.p. 116° (lit.⁷¹, 120°).

Ethyl 3-(2-Nitrophenyl)-2-oxopropanoate (79)

(a) A solution of 3-(2-nitrophenyl)-2-oxopropanoic acid (80) (1.1 g; 0.005 mol) in anhydrous ethanol (15.0 ml) was treated with concentrated sulphuric acid (0.5 ml) and the mixture was heated under reflux with the exclusion of atmospheric moisture for 6 h. The resulting clear red solution was evaporated to one third of its original volume and then cooled (ice-water bath) and treated with water (25.0 ml). The mixture was treated with diethyl ether (3 x 25.0 ml) and the combined organic extracts were washed with 10% w/v aqueous sodium hydrogen carbonate solution

(3 x 5.0 ml) then with water (3 x 10.0 ml) to afford ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) as a clear yellow oil (1.0 g; 80%), b.p. 150°/0.08 mm Hg (lit.⁷⁰, m.p. 69°), ν_{\max} 3440 (OH), 1780-1680 br (CO) and 1525 and 1350 (NO₂) cm⁻¹, δ_{H} (CDCl₃) 8.14 (1H, dd, J_{ortho} 8Hz, J_{meta} 2Hz, ArH), 7.64-7.25 (3H, m, ArH), 4.51 (2H, s, CH₂), 4.36 (2H, q, J 7Hz, CH₂CH₃) and 1.37 (3H, t, J 7Hz, CH₂CH₃).

(b) Ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) was prepared by the potassium ethoxide catalysed condensation of 2-nitrotoluene (27f) with diethyl oxalate as described by Wislicenus and Thoma⁷⁰ as an oil (yield 71%), identical (i.r. and ¹H n.m.r. spectra) to a sample synthesised in (a) before.

Ethyl 3-(2-Nitrophenyl)-2-oxopropanoate Phenylhydrazone (82b)

A solution of ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) (0.48 g; 0.002 mol) and phenylhydrazine (0.22 g; 0.002 mol) in ethanol (10.0 ml) was heated under reflux for 3 h. The mixture was evaporated to afford an orange oil (0.69 g) which solidified on standing and was triturated with toluene to yield ethyl 3-(2-nitrophenyl)-2-oxopropanoate phenylhydrazone (82b) (0.47 g; 71%) as yellow crystals, m.p. 99° (lit.⁷⁰, 104°) (from toluene), ν_{\max} 3320 (NH), 1695 (CO) and 1515 and 1335 (NO₂) cm⁻¹.

3-(2-Nitrophenyl)-2-oxopropanamide (79; CONH₂ for CO₂Et)

Ethyl 3-(2-nitrophenyl)-2-oxopropanamide (79; CONH₂ for CO₂Et) was prepared by the reaction of ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) with ammonia as described by Wislicenus and Thoma⁷⁰ (yield 52%) m.p. 162° (from glacial acetic acid) (lit.⁷⁰, 166°).

Ethyl 3-(2-Nitrophenyl)-2-(N-phenylimino)propanoate (82a)

Ethyl 3-(2-nitrophenyl)-2-(N-phenylimino)propanoate (82a) was prepared by the reaction of ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) with aniline as described by Wislicenus and Thoma⁷⁰ (yield 88%) m.p. 89° (lit.⁷⁰, 92°).

2-Nitrophenylacetic Acid (22)

The red solution of ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) (2.4 g; 0.01 mol) in 2% w/v aqueous sodium hydroxide solution (20.0 ml) was stirred at 5-10° (ice-bath) for 1 h. then treated with 6% w/v aqueous hydrogen peroxide solution (40.0 ml) and the mixture stirred at room temperature for a further 4 h. The mixture was acidified with concentrated hydrochloric acid and filtered to give 2-nitrophenylacetic acid (22) (1.2 g; 65%) m.p. 138° (lit.⁷⁵, 141°) identical (m.p., mixed m.p. and i.r. spectrum) to an authentic sample.

The Attempted Condensation of 2-Nitrotoluene (27f) with
Dimethylformamide Dimethylacetal followed by Ethyl
Oxalyl Chloride

A solution of 2-nitrotoluene (27f) (3.4 g; 0.025 mol) in anhydrous dimethylformamide (10.0 ml) was stirred and treated dropwise with dimethylformamide dimethyl acetal (3.3 g; 0.028 mol) and the mixture was heated under reflux with the exclusion of atmospheric moisture for 26 h. The dimethylformamide was removed from the resulting red solution by distillation under reduced pressure to afford the enamine (38f) as a viscous red oil (5.7 g). This was dissolved in anhydrous toluene (25.0 ml) and the solution treated dropwise with stirring with triethylamine (2.5 g; 0.025 mol) followed by ethyl oxalyl chloride (3.4 g; 0.025 mol). The mixture was stirred and heated under reflux with the exclusion of atmospheric moisture for 15 h. The resulting dark mixture was cooled, treated with water (15.0 ml) and filtered to remove some tarry material. The two phase filtrate was separated and the organic phase evaporated to give a brown oil (4.09 g). This was dissolved in 1,4-dioxane (25.0 ml) and water (8.0 ml) and the mixture heated under reflux for 18 h. The resulting brown solution was evaporated to afford a brown oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) and water (2 x 10.0 ml) and evaporated to

yield a brown oil (2.6 g) which was flash-chromatographed over silica.

Elution with toluene gave unreacted 2-nitrotoluene (27f) (0.66 g; 19%) identical (i.r. spectrum) to an authentic sample.

Further elution with toluene:methylene chloride, through ethyl acetate to methanol yielded a series of oils and gums (total 1.6 g) whose t.l.c. in methylene chloride over silica showed them to be complex close running mixtures from which no identifiable material could be obtained.

Ethyl 3-Bromo-3-(2-nitrophenyl)-2-oxopropanoate (81)

Ethyl 3-bromo-3-(2-nitrophenyl)-2-oxopropanoate (81) was prepared by the reaction of ethyl 3-(2-nitrophenyl)-2-oxopropanoate (79) with bromine in 1,2-dimethoxyethane and was obtained as an oil (yield 90%) (lit.⁷⁰, m.p. 82°) ν_{\max} 3470 (OH) and 1790 and 1690 (CO) cm^{-1} , δ_{H} (CDCl_3) 8.16-7.25 (4H, m, ArH), 6.95 (1H, s, CH), 4.34 (2H, q, J 7Hz, CH_2CH_3) and 1.40 (3H, t, J 7Hz, CH_2CH_3).

APPENDIXGeneral Experimental Data

Infrared spectra were recorded for nujol suspensions or thin films using a Perkin-Elmer 781 spectrophotometer. I.r. bands were strong and sharp unless specified as w (weak) or br (broad).

Ultraviolet spectra were measured for solutions in ethanol using a Perkin-Elmer 402 spectrophotometer.

¹H N.m.r. spectra were measured in the stated solvent at 80 MHz or 200 MHz using Brucker WP-80SY and WP-200SY spectrometers. Signals were sharp singlets unless specified as br (broad); d = doublet; t = triplet; q = quartet; m = multiplet.

Mass spectral and accurate mass data were obtained using A.E.I. MS-902 and Kratos MS 50TC instruments. Fast atom bombardment (F.A.B.) mass spectra were measured for chloroform thioglycerol matrices using a Kratos MS 50TC instrument.

Microanalyses were determined on a Carlo-Erba Strumentazione Elemental Analyser MOD 1106. Melting points (m.p.) of all analytical samples were determined on a Kofler hot-stage and are uncorrected.

All yields are based on unrecovered starting-material and all organic extracts were dried over anhydrous magnesium sulphate prior to evaporation under reduced pressure. Solvents were of technical grade, unless otherwise specified and unless otherwise indicated light petroleum had b.p. 60-80°.

Thin layer chromatography (t.l.c.) was carried out over plastic coated silica sheets (Polygram SilG-UV₂₅₄) and flash-chromatography was carried out over silica (Merck Kieselgel 60: Art. 9385). Medium pressure liquid chromatography was carried out at 60-100 p.s.i. (metering pump) over silica (Merck Kieselgel 60: Art. 9385).

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